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ACUTE AND CHRONIC LEUKEMIA

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DIAGNOSIS

1. UNUSUAL SKELETAL CHANGES FROM ACUTE LEUKEMIA DURING CHILDHOOD.

Riebel T, Kabisch H
Universitatskinderklinik Hamburg, Rontgenabteilung, Martinstr. 52, D-2000 Hamburg 20, W. Germany
ROEFO; 135(1):12-16 1981

Five cases of pediatric leukemia were described. Patients ranging in age from 3.5 to 11 yr, developed pain, redness, and swelling variously in the foot, elbow, shoulder, forearm, and knee. Symptoms suggested osteomyelitis or rheumatic disease. All cases developed similarly. After several wk x-rays showed 'moth-eaten' light spots in the bone, with erosion of the corticalis and periosteal reaction. Patients had fever. Erythrocyte sedimentation was accelerated. In three cases leukemia was not discovered until after changes in the bone had occurred. In one case occurring after remission from leukemia, a lesion appeared in the olecranon of the ulna. Later lesions developed in the fibula, a finger, the metaphyses of the femur and radius, and in the mid-facial bones. Necrosis of bone, together with the growth of leukemic cells in the bone marrow, was suggested as the cause of pain. Improvement in hematologic symptoms of leukemia was accompanied by an improvement in skeletal symptoms. Recurrence of the leukemia was sometimes accompanied by recurrence of the original bone lesions or new lesions in different locations. (16 Refs) (In GER)

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2. CHRONIC LYMPHOCYTIC LEUKAEMIA: PROPOSALS FOR A REVISED STAGING SYSTEM.

Binet JL, Catovsky D, Chandra P, Dighiero G, Montserrat E, Rai KR, Sawitsky A
(c/o Sawitsky) Long Island Jewish-Hillside Medical Center, New Hyde Park, NY, 11042
Br J Haematol; 48(3):365-367 1981

The staging classification system proposed by the International Workshop of chronic lymphocytic leukemia (CLL) and its prognostic value are discussed. The proposal is the result of a multivariate analysis of 900 CLL patients that demonstrated three survival curve patterns. Patients with anemia and/or thrombocytopenia had the poorest prognosis and were placed in Group C. The prognosis of the remaining patients depended on the number of areas of lymphoid enlargement, ie, spleen, liver, and lymph nodes in the cervical, axillary, and inguinal regions. Patients with involvement of greater than three areas had the best prognosis and were placed in Group A; patients with three or more involved areas constituted Group B and were of intermediate prognosis. It is recommended that the A, B, C classification be integrated with the Rai system to permit the reevaluation of biological characteristics of subset populations of CLL patients. The advantages of the proposed classification in treatment planning and research are discussed. (16 Refs)

3. POSITIVE IDENTIFICATION OF HUMAN LEUKAEMIC CELLS WITH SCANNING IMMUNO-ELECTRON MICROSCOPY, USING ANTIBODY COATED POLYSTYRENE (LATEX) BEADS AS MARKERS.

Gamliel H, Polliack A
(c/o Polliack) Dept. Haematology, Hadassah Univ. Hosp., Kiryat Hadassah, P.O. Box 12000, IL-91 120 Jerusalem, Israel
Scand J Haematol; 26(4):297-305 1981

Scanning immuno-electron microscopic labeling techniques were successfully used to identify a variety of leukemia-lymphoma cells. Anti-T, -B and -common type acute lymphoblastic leukemia (ALL) antisera were covalently conjugated to polystyrene latex spheres by means of glutaraldehyde. Peripheral blood mononuclear cells obtained from healthy individuals and from patients with T-type ALL, B-type chronic lymphocytic leukemia (CLL), acute and chronic non-lymphoblastic leukemias (ANLL) and cultured leukemia-lymphoma cells were incubated with the above antisera-latex conjugates. Positively labeled cells were easily identified by the presence of latex spheres on their surfaces. Cross reactivity of the antisera used and non-specific attachment of the markers were infrequently encountered. The results of this study confirm earlier scanning electron microscopic reports indicating that different leukemic cells have characteristic surface features and show that scanning immuno-electron microscopy (SIEM) can readily be applied to the study of human leukemic cells. (Author abstract) (34 Refs)

4. CYTOCHEMISTRY AND MEMBRANE MARKERS IN ACUTE LYMPHATIC LEUKAEMIA (ALL).

Huhn D, Thiel E, Rodt H, Andreeva P
Medizinische Klinik III, Grosshadern, Marchioninistr. 15, D-8000 Munchen 70, W. Germany
Scand J Haematol; 26(4):311-320 1981

One hundred thirty-six patients suffering from ALL were subdivided into 5 subtypes (C-ALL, C/T-ALL, pre-T-ALL, B-ALL) according to rosetting tests and using specific antisera directed against membrane antigens. In addition, leukemic blasts of all patients were investigated according to morphological and cytochemical criteria. In APh and ANAE, indices and the percentages of cases showing a granular staining pattern were high in pre-T- and in T-ALL, but low in C/T- and in C-ALL. PAS-staining, conversely, was more pronounced in C/T- and C-ALL. APh proved to be more discriminative for recognition of the T- and Pre-T-ALL subgroups than ANAE, but ANAE-cytochemistry may be useful to detect contaminating normal T-lymphocytes in ALL. Receptors for C3 were more frequent in C- and in T-ALL than in C/T- and in pre-T-ALL, receptors for Fc were distributed equally among all subtypes. Positivity of C3-and Fc-receptors was not correlated with cytochemical results. Morphological criteria were not sufficient for subclassification of ALL; the combination of APh- and PAS-staining, however, is valuable to differentiate between C-subgroups and T-subgroups. (Author abstract) (36 Refs)

5. ULTRASTRUCTURAL CYTOCHEMICAL PROSPECTIVE STUDY OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA: DETECTION OF PEROXIDASE ACTIVITY IN PATIENTS FAILING TO RESPOND TO TREATMENT.

Reiffers J, Dermendrail V, Larrue J, Villenave I, Bernard P, Boisseau M, Proustet A
Service de Medecine Interne et des Maladies du Sang, Hopital du Haut Leveque, Groupe Hospitalier Sud, Avenue de Magellan, 33604 Pessac, France
Cancer; 48(4):927-931 1981

Ultrastructural cytochemical studies revealed peroxidase activity in 5 of 25 adult patients with apparent null lymphoblastic leukemia (ALL) in whom the peroxidase reaction studied with light microscopy was negative. None of these five patients responded to a chemotherapy regimen used for adult ALL. The importance of ultrastructural cytochemistry which allows the recognition of myeloblastic differentiation in undifferentiated blast cells is also demonstrated. The correct classification of such cases may be important for prognosis because they appear to be resistant to the chemotherapy used in treating ALL. (Author abstract) (14 Refs)

6. MEGAKARYOBLASTIC LEUKEMIA PRESENTING AS ACUTE MYELOFIBROSIS - A STUDY OF FOUR CASES WITH THE PLATELET-PEROXIDASE REACTION.

Bain BJ, Catovsky D, O'Brien M, Prentice HG, Lawlor E, Kumaran TO, McCann SR, Matutes E, Galton DA
(c/o Catovsky) MRC Leukaemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 0HS, England
Blood; 58(2):206-213 1981

Acute myelofibrosis (AM) or malignant myelosclerosis is a myeloproliferative syndrome in which bone marrow fibrosis is associated with a proliferation of immature myeloid cells. In four patients with typical AM, investigated by the platelet-peroxidase reaction at ultrastructural level, the blast cells were found to be megakaryoblasts. One patient, treated with the drug combination DAT, achieved a complete remission of 5 mo duration. This study supports the view that megakaryoblastic leukemia is the most frequent underlying cause of AM and proposes that it should be classified as a form of acute myeloid leukemia. (Author abstract) (23 Refs)

7. HEMATOLOGICAL AND CLINICAL MANIFESTATIONS OF THE INITIAL STAGES OF CHRONIC MYELOCYTIC LEUKEMIA.

Tokuhiro H, Hirasawa Y, Kuto F, Nagaoka T, Hayashi M
Dept. Internal Medicine, Kitasato Univ. Sch. Medicine, Kitasato, Japan
Rinsho Ketsueki; 22(4):433-443 1981

Clinical features of the initial stage of chronic myelogenous leukemia (CML) were investigated in 48 patients (25 men, 23 women), 47 of whom had the Philadelphia chromosome. One feature especially common among men with the CML was peptic ulcer (16/48); the mean age of the men with CML and peptic ulcers that were observed prior to the diagnosis of CML was higher than that of the men who had CML but not peptic ulcers. Repeated radiologic examinations for the peptic ulcers were thought to be associated with the cause of the CML. WBC counts in 9/16 patients who were followed hematologically prior to diagnosis of CML remained at approx 10,000 count levels for 3.5-5.9 mo and then increased to 30,000 levels over a 1.5-5.7 mo period. The increases in the WBC counts were not simply linear but showed periods of decrease throughout the general increasing trend. Increased numbers of basophils were also observed from the early stages of the disease. (20 Refs) (In JPN)

8. SIGNIFICANCE OF NON-STANDARD PHILADELPHIA CHROMOSOMES IN CHRONIC GRANULOCYTIC LEUKAEMIA.

Potter AM, Watmore AE, Cooke P, Lilleyman JS, Sokol RJ
Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN, England
Br J Cancer; 44(1):51-54 1981

One hundred and nineteen unselected and similarly treated patients with Ph1-positive chronic granulocytic leukemia (CGL) had the precise nature of their chromosome rearrangements producing the Ph1 studied to determine whether this had any clinical relevance. Eighteen (15%) did not have the usual 9/22 translocation and these, by life-table analysis, had a significantly shorter benign phase of t heir disease than the others (p less than 0.01). It further appeared that possession of a non-standard Ph1 was related to age, in that whereas only 24 patients were over 60 at diagnosis, 9 (33%) had a non-9/22 translocation (p less than 0.01). As the duration of the benign phase seemed to be shorter in those over 60 irrespective of Ph1 type (p less than 0.01), the question arose whether non-standard Ph1 chromosomes were simply occurring in older patients or whether they were affecting prognosis independently. Their independent effect was suggested by the 11 patients under 60 with a non-9/22 Ph1 who still had a significantly shorter benign phase than the 84 of similar age with a standard Ph1 (p less than 0.01). It is concluded that the myeloid karyotype can provide prognostic as well as diagnostic information in patients with CGL. (Author abstract) (7 Refs)

9. CULTURE OF BONE MARROW REVEALS MORE CELLS WITH CHROMOSOMAL ABNORMALITIES THAN THE DIRECT METHOD IN PATIENTS WITH HEMATOLOGIC DISORDERS.

Knuutila S, Vuopio P, Elonen E, Silmes M, Kovanen R, Borgstrom GH, De la Chapelle A
Dept. Medical Genetics, Univ. Helsinki, Haartmaninkatu 3, 00290 Helsinki 29, Finland
Blood; 58(2):369-375 1981

The effect of short-term culture on the type and frequency of chromosomal aberrations found in bone marrow cells from patients with hematologic disease was evaluated. The classic direct method (1-2 hr incubation) was compared with methods involving culture for 1-4 days with or without methotrexate. Data on 32 samples from 21 patients in whom an abnormal clone was found indicated that on 18 occasions, culture yielded a higher proportion of cells belonging to the abnormal than to the normal clone. In 10 of those cases, the difference was statistically significant (p less than 0.05). The reverse situation was seen on six occasions, none of which was statistically significant. On four occasions, the culture methods disclosed a clonal abnormality that would not have been detected if the direct method alone had been used. The phenomenon occurred in chronic myeloid leukemia, myeloid and lymphoid acute leukemia, and preleukemic conditions. It affected clones with different cytogenetic abnormalities such as 5q-, t(8;21) and i(17q). In one instance, sister chromatid staining after BUdR incorporation indicated that both cytogenetically normal and abnormal (5q-) mitoses were in their second division after 2 days in culture. The implication of these studies is that to improve the chances of detecting cytogenetically abnormal cells, bone marrow cells should be cultured. Examination of as many mitoses as possible after culture for 1-4 days may reveal abnormal clones that are sparsely represented. Finally, results obtained with different methods are not directly comparable. (Author abstract) (11 Refs)

10. ACUTE LYMPHOCYTIC AND MYELOMONOCYTIC LEUKEMIA ASSOCIATED WITH LOW PLATELET COUNT S AND 21Q- MARKER CHROMOSOME.

Alimena G, Dallapiccola M, De Cuia MR, Mandelli F, Mitelman F
Dept. Hematology, Univ. Rome, Via Chieti 7/Via Lancisi 3, I-00161 Rome, Italy
Hum Genet; 57(3):329-331 1981

The case histories of two patients (1 man and 1 woman) with acute lymphocytic and acute myelomonocytic leukemia who had a 21q- marker chromosome are reported. Both patients were thrombocytopenic at diagnosis and during the course of the disease. The platelet count was 65 x 10(9)/liter and 85 x 10(9)/liter, respectively. The deleted segment of chromosome 21 was not translocated to any other chromosome of the complement. It was concluded that 21q- marker is not related to an increased platelet count, nor limited to primary thrombocytopenia. (11 Refs)

11. ANALYSIS OF C BANDS IN HAEMATOLOGICAL DISORDERS.

Labal de Vinuesa M, Slavutsky I, Larripa I, De Salum SB
Instituto de Investigaciones Hematologicas 'Mariano R. Castex', Academia Nacional de Medicina, Pacheco de Melo, 3081, Capital Federal (1425), Argentina
Sangre (Barc); 26(3):319-323 1981

The variations in size and form of heterochromatin observed in normal populations are called polymorphisms. In patients with malignancies the number of such variations is increased. A study of the heteromorphism of chromosomes 1, 9, and 16 was performed in 20 normal subjects, in 32 patients with hematological malignancies and in 10 patients with preleukemia. Significant differences were found with respect to the control group in leukemia (p less than 0.001) and lymphoma (p less than 0.05) but not in preleukemia. Chromosome 1 was characteristically involved, this being the only pair with differences with regard to the control group in leukemia and lymphoma; the pericentric inversion of the chromosome was the most remarkable finding. (Author abstract) (14 Refs) (In SPA)

12. C-BANDING STUDIES IN PATIENTS WITH PH(1)+ CHRONIC GRANULOCYTIC LEUKAEMIA.

Rajasekariah P, Garson OM
(c/o Garson) Cytogenetics Unit, Saint Vincent's Hosp., Fitzroy, Victoria, Australia 3065
Pathology; 13(2):197-203 1981

The bone marrow chromosomes of 15 patients with Ph(1)+ chronic granulocytic leukemia were studied, using both G- and C-banding. In all cases the Ph1 chromosome was formed by the translocation between chromosomes 9 and 22 and the material from chromosome 22 was found to be translocated randomly onto one or other of the pair of 9 chromosomes. Preliminary results suggest that when the translocation was on the 9 chromosome having a smaller C-band, additional abnormalities occurred in blastic transformation, whereas when the 9 chromosome with the larger C-band was involved in the translocation, additional abnormalities were not found in blastic transformation. These observations require confirmation from a larger series. C- banding also showed that there was a greatly increased heteromorphism of the C-band areas of the chromosome pair 9 in this disease, and an increased heteromorphism in the C-bands of chromosome pair 1, when compared with a control group. (Author abstract) (20 Refs)

13. STUDIES OF CELLULAR PROLIFERATION IN INFANTILE LEUKEMIA BY IMPULSE CYTOPHOTOMETER (I.C.P.).

Iwama M
Dept. Pediatrics, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nippon Gan Chiryo Gakkai Shi; 16(1):56-63 1981

Nucleic DNA distribution of leukemic cells from peripheral blood and bone marrow was determined with the aid of impulse cytophotometry (ICP) after staining the cells with ethidium bromide. The leukemic cells were obtained from 2-18-yr-old children with acute lymphocytic leukemia (5 cases), acute myelocytic leukemia (4), or leukocytic reticulosarcoma (1). During the onset or relapse of the disease, the DNA histograms of many cases showed high peaks of 2N cells and low peaks of 4N cells. Changes in patterns of histograms were examined after administration of vincristine (V), cytosine arabinoside (CA), or neocarzinostatin (NC). When V was injected, the cells accumulated in the S, G2-M phases. When CA was injected, the cells accumulated in the early S region, G1-S boundary at first (hr 24), then moved to late S or G2-M phases (hr 72). When NC was injected, the cells accumulated in the 4N region. Histograms of the patients refractory to chemotherapy did not show any remarkable changes. The results suggested that combination chemotherapy might be chosen more effectively on the basis or in vivo perturbation of the cell cycle. (23 Refs) (In JPN)

14. LACK OF PROGNOSTIC VALUE OF THE THYMIDINE-LABELLING INDEX IN ADULT ACUTE LEUKAEMIA.

Sewell RL, Lister TA, Johnson SA, Crowther D
Imperial Cancer Res. Fund, Dept. Medical Oncology, St. Bartholomew's Hosp., London EC1A 7BE, England
Br J Cancer; 44(1):55-62 1981

A study has been made of the thymidine labeling index (TLI) of marrow blast cells in 201 adults with untreated acute leukemia. There was no significant difference between the TLI in 172 patients with acute myeloblastic leukemia and 29 patients with acute lymphoblastic leukemia. The TLI did not correlate with the age, sex, peripheral-blood or marrow blast-cell count, or the platelet count at presentation. In neither acute myeloblastic leukemia nor acute lymphoblastic leukemia was there any correlation between the TLI and the response to the initial therapy, the duration of the first complete remission or survival. (Author abstract) (30 Refs)

15. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITIES AND GLUCOCORTICOID RECEPTORS IN LEUKAEMIA.

Sasaki R, Takaku F, Aoki T, Bollum FJ, Saito T, Dan S
Dept. Haematology, Jichi Medical Sch., 3311-1 Yakushiji Minamikawachi-Machi, Kawachigun, Tochigi 329-04, Japan
Br J Cancer; 44(1):63-67 1981

The relation between terminal deoxynucleotidyl transferase (TdT) activity, glucocorticoid (GC) receptors and the effect of vincristine-prednisolone (VP) therapy on fresh leukemia cases was examined. Five of six TdT+ leukemias showed high levels of GC receptors and a favorable response to VP therapy, whereas one acute lymphoblastic leukemia and three of chronic myelogenous leukemia cases in blast crisis with no TdT activity showed low level of GC receptors and poor response to VP therapy. Significant correlation ($r = 0.821$, p less than 0.01) was observed between TdT activity and the number of GC receptor sites in these cases. Chi square test showed significant difference (p less than 0.01) between TdT+ and TdT- leukemias in the effect of VP. A significant difference (p less than 0.01) was also observed between VP-effective and ineffective leukemias in the number of GC-receptor sites by unpaired t test. Therefore GC receptors may be responsible for the effect of VP on TdT+ leukemias. (Author abstract) (18 Refs)

16. CHARACTERISTICS OF THE BLASTIC CRISIS WITH TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE POSITIVE BLASTS IN CHRONIC GRANULOCYTIC LEUKEMIA.

Sawada H, Tashima T, Konishi H, Usui T, Kenkichi K, Shigeru OS, Kamada N, Uchino H
First Div. Internal Medicine, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Nippon Ketsueki Gakkai Zasshi; 44(4):872-880 1981

In 32 patients in the blastic phase of chronic granulocytic leukemia (CGL) the terminal deoxynucleotidyl transferase (TdT) activity was measured. TdT positive blasts were seen in 10/32 patients. Those whose blasts had a high TdT activity had an abrupt onset of blast crisis. When hematologic blastic crisis occurred, the TdT positive group in general had a more profound thrombocytopenia, leukocytosis, a great number of blasts, and a decrease in size of the spleen, compared to the TdT negative group. The TdT positive group showed a favorable response to the chemotherapy, and the survival time after the blastic crisis was longer. TdT may prove to be a marker capable of predicting a favorable response to the chemotherapy. (Author abstract) (29 Refs)

17. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE-CONTAINING CELLS IN PERIPHERAL BLOOD: IMPLICATIONS FOR THE SURVEILLANCE OF PATIENTS WITH LYMPHOBLASTIC LEUKEMIA OR LYMPHOMA IN REMISSION.

Froehlich TW, Buchanan GR, Cornet JM, Sartain PA, Smith RG

(c/o Smith) Cancer Center, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX. 75235

Blood; 58(2):214-220 1981

An indirect immunofluorescence assay was used to quantitate TdT-containing (TdT+) cells in the mononuclear WBC fraction of peripheral blood from normal subjects and patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). In normal children (10) and adults (10), 0.036% +-0.014% (mean +- SD) and 0.030% +-0.015% TdT+ cells were found. In peripheral bloods from 10 children receiving chemotherapy for tumors other than ALL or LL, 0.040% +-0.039% TdT+ cells were found. Serial determinations were performed on 15 patients with ALL or LL who were in clinical remission. Eight of these patients remained in continuous remission and always had fewer than 0.11% TdT+ cells in their peripheral blood. Three patients who developed systemic relapse were found to have progressively rising numbers of TdT+ cells in their peripheral blood prior to clinical evidence of relapse. All three of these patients had greater than 0.1% TdT+ cells in their peripheral blood from 3 to 8 wk prior to clinical relapse. In three other patients, localized extramedullary relapse developed, but no trend was found on serial TdT determinations. Thus, the indirect immunofluorescence assay for TdT detects a small population of cells in normal peripheral blood. In patients with ALL, progressive increases above this normal level were associated with subsequent bone marrow relapse. (Author abstract) (17 Refs)

18. MURAMIDASE IN RELATION TO MORPHOLOGIC TYPES OF ACUTE LEUKAEMIA.

Dube RK, Sahu BB, Singh VP, Srivastava A, Dube B

Dept. Pathology, Inst. Medical Sciences, Banaras Hindu Univ., Varanasi 221005, India

Indian J Med Res; 73:938-940 1981

Serum muramidase and urinary muramidase levels were correlated with different morphologic types of acute leukemia (61 cases) according to FAB classification. Elevated serum enzyme levels and an appreciable degree of muramidasuria were seen in every case of M4 and M5 types of acute myeloid leukemia. M1, M2 and M6 types showed much variability; half of them had serum levels within normal range. M3 type (2 patients) showed normal muramidase levels. Among patients with acute lymphoblastic leukemia, serum muramidase was depressed in 71% of cases; L1 and L2 types showed no significant difference. (Author abstract) (7 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

19. ANALYSIS OF CELL-SURFACE ANTIGEN OF HAIRY CELL LEUKEMIA (HCL).

Ogasawara M, Ishii Y, Kikuchi K, Aikawa K, Mikuni C

First Dept. Pathology, Sapporo Medical Coll., Sapporo-shi, Hokkaido, 060, Japan

Igaku Ayumi; 116(1):29-31 1981

One patient with cell surface Ig-positive HCL and another patient with HCL shown to have B cell markers by immunoprecipitation with anti-HCG and anti-B serum were seen. An antiserum specific for hairy cells (AHCS) was obtained by immunizing rabbits with 2 x 10(7) hairy cells iv. The absorbed AHCS for both patients diluted 80-160x produced 100% fluorescein isothiocyanate-stained cells, but peripheral blood (T, B cells) and the two B-cell lymphoid leukemias were not responsive. Some tonsil B cells responded with fluorescence of 12-27%, but no T cells responded. Various leukemia cells other than the hairy cells barely r esponded to the lymphocytes, nor did they respond to the granulocyte or monocyte leukemia cells. The unabsorbed antiserum had four major peaks, with mol wt of 110,000-120,000, 94,000-96,000, 48,000-50,000, and 30,000-34,000 for I, II, III, and IV. In the absorbed AHCS, peaks II and IV disappeared, leaving only I and II. The antigen at peak III is considered to differ from histocompatibility antigen (HLA) because it is not absorbed by anti-HLA or anti-beta2m. This antigen is considered to be the one that is differentiated from that of B cells which characterizes the hairy cell. The antigen at peak IV was also obtained by adding anti-B serum to the B cell lysates and the peak IV antigen that disappeared was considered to be an Ia-like antigen on the hairy cell. Antisera obtained from the two HCL patients were shown to recognize the same antigen. (Author abstract) (12 Refs) (In JPN)

20. ABSENCE OF COMMON ALL ANTIGEN ON NORMAL BIPOTENT MYELOID, ERYTHROID, AND GRANULOCYTE PROGENITORS.

Clavell LA, Lipton JM, Bast RC, Kudisch M, Pesando J, Schlossman SF, Ritz J

Instituto Hematologico Oncologico Pediatrico, Hospital Universitario de Ninos, Recinto de Ciencias Medicas, G.P.O. Box 5067, San Juan, PR, 00936

Blood; 58(2):333-336 1981

The presence of the common acute lymphoblastic leukemia antigen (CALLA) on leukemic cells from the great majority of patients with non-T-cell acute lymphoblastic leukemia and chronic myelogenous leukemia in blast crisis suggests that CALLA could be a differentiation antigen expressed by normal lymphoid and myeloid stem cells. Treatment with a murine monoclonal anti-CALLA antibody and complement lysed CALLA-positive leukemic cells quantitatively, whereas similar treatment of nucleated cells from peripheral blood and bone marrow failed to affect the expression, in semisolid culture, of CFU-G/E, BFU-E, CFU-E, or CFU-C. These data suggest that CALLA is not a normal differentiation antigen of the myeloid bipotent cell or its committed progenitors. (Author abstract) (20 Refs)

21. HETEROGENEITY OF B-CELL LEUKEMIAS DEMONSTRATED BY THE MONOCLONAL ANTIBODY FMC7.

Catovsky D, Cherchi M, Brooks D, Bradley J, Zola H
MRC Leukaemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 OHS, England
Blood; 58(2):406-408 1981

A new monoclonal antibody, FMC7, was studied in 68 patients with chronic B-cell leukemia. All 17 cases of prolymphocytic leukemia (B-PLL) and 8/9 of hairy-cell leukemia were positive. In contrast, FMC7 was negative in 32 of 38 chronic lymphocytic leukemias (B-CLL; p less than 0.001) and four cases of B-cell lymphoma. Four of the six positive B-CLL cases were in 'prolymphocytoid' transformation; two of them had bright membrane Ig (SmIg) staining and may represent an intermediate form between B-CLL and B-PLL. Although there was a tendency for the intensity of the immunofluorescence reaction with FMC7 and SmIg to change in parallel, FMC7 did not correlate with any Ig class. In addition, almost all FMC7-negative B-CLL had weak expression of SmIg. FMC7 is different from other monoclonal antibodies raised against B-lineage cells in that it recognizes only some subsets, presumably those at a late stage of maturation. This property confers diagnostic potential to this reagent and may contribute to the better characterization of the B-cell neoplasias. (Author abstract) (14 Refs)

22. NATURAL KILLER (NK) ACTIVITY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Tanaka Y
Dept. Pediatrics, Hiroshima Univ. Sch. Medicine, Hiroshima 734, Japan
Hiroshima J Med Sci; 30(2):127-133 1981

The NK activity of peripheral blood mononuclear cells from 20 children (aged 1-13 yr) with acute lymphoblastic leukemia at the time of diagnosis and during chemotherapy was investigated. Before chemotherapy, in five children the NK activity increased with the effector to target cell (E/T) ratio; in three children the NK activity was within the normal range, and in two it was significantly lower. Bone marrow cells aspirated from iliac crests in these five patients showed no NK activity against K 562 target cells. NK activity decreased after the start of induction therapy with vincristine and prednisolone. After complete remission, NK activity returned to normal levels (higher than at the time of diagnosis in four patients). During maintenance chemotherapy, NK activity in 15 children with ALL in continuous complete remission was 44.9 +-16.9% compared with 40.8 +-11.5% in 20 healthy children and 41.3 +-14.2% in 26 healthy adults. (36 Refs)

CHEMOTHERAPY

23. HIGH-DOSE COMBINATION CHEMOTHERAPY FOR ACUTE NONLYMPHOBLASTIC LEUKEMIA IN ADULTS.

Glucksberg H, Cheever MA, Farewell VT, Fefer A, Sale GE, Thomas ED
(c/o Fefer) Dept. Medicine, Univ. Washington Sch. Medicine, BB1025 Health Sciences, Seattle, WA, 98195
Cancer; 48(5):1073-1081 1981

One hundred thirty-nine consecutive unselected adults with acute nonlymphoblastic leukemia were treated with a high-dose chemotherapeutic remission-induction regimen consisting of daunomycin (70 mg/m2 (m2) iv on days 1,2,3), cytosine arabinoside (100 mg/m2 iv every 12 hr), 6-thioguanine (100 mg/m2 po every 12 hr), prednisone (40 mg/m2 daily), all given on days 1 through 7, and vincristine (1 mg/m2 iv on days 1 and 7). Supportive care consisted of broad spectrum antibiotics for fever in the presence of granulocytopenia and prophylactic platelet transfusions. The complete remission (CR) rate was 60%. The median number of days to CR was 30. Fifty-eight of 77 (75%) patients under age 50 and 26 of 62 (42%) patients over age 50 attained CR. Despite the use of a relatively large dose of daunomycin and monthly maintenance chemoth erapy, the median remission duration was only 39 wk and the median survival 64 wk. Most patients who failed to achieve CR died early -77% of deaths occurred within the first 6 wk. Infections accounted for the increased mortality in patients over age 50. Thirty-seven percent of patients over age 50 died of infections whereas only 10% under age 50 did so (p less than 0.001). Seven percent of the patients died of fungal infection during attempted remission induction. The incidence of resistance of the leukemia to the remission-induction regimen was low (8%). (Author abstract) (48 Refs)

24. INTERRUPTION OF ANTIBLASTIC THERAPY IN ADULTS WITH ACUTE LYMPHOID LEUKEMIA (MEETING ABSTRACT).

Amadori S, Meloni G, Aloe Spiriti MA, Mandelli F
Universita degli Studi di Roma, Rome, Italy
Tumori; 67(2,SupplA):47 1981

The literature is lacking in useful information regarding the optimal duration of treatment of adult acute lymphatic leukemia patients (ALL) in complete remission (CR). As of June, 1978, a total of 70 adult patients (greater than 15 yr) with ALL were treated with a therapy protocol composed of : vincristine and prednisone +/- daunomycin and/or asparaginase as induction; mercaptopurine and methotrexate + periodic reinductions with vincristine and prednisone as maintenance; intrathecal methotrexate alone or combined with cranial radiotherapy as neuromeningeal prophylaxis. CR was achieved in 47 patients (67.1 per cent); in 16 of them (34 per cent) each treatment was interrupted after 30-40 mo of continuous complete remission (CCR). With a median off-therapy follow-up of 18 mo (range 4-60) there have been to date 4 recurrences after 4-15 mo from stop therapy (2 marrow, 1 marrow + testis, 1 marrow + skin + meninges). 3 principal considerations arise from our results: 1) long remissions can be obtained in about one-third of adult patients with ALL who respond to induction therapy; 2) risk of recurrence is greater during the first yr following suspension of treatment; 3) initial leukocytosis greater than 50,000/mm3 significantly reduces the probability of long-term remission. (no Refs) (In ITA)

25. TREATMENT OF ACUTE LEUKEMIA IN RELAPSE WITH 4'(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE (AMSA) IN COMBINATION WITH CYTOSINE ARABINOSIDE AND THIOGUANINE.

Arlin ZA, Flomenberg N, Gee TS, Kempin SJ, Dellaquila C, Mertelsmann R, Straus DJ, Young CW, Clarkson BD
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Clin Trials; 4(3):317-321 1981

Thirty-seven patients with acute leukemia in relapse were treated with a three-drug combination that included a 3-or 4-day course of 4'(9-acrylamidinylamino)methanesulfon-m-anisidide (AMSA) with total doses ranging from 600 mg/m2 (m2)

to 740 mg/m2 iv, cytosine arabinoside 25 mg/m2 iv, followed by 200 mg/m2 by continuous infusion daily for 5 days, and thioguanine 100 mg/m2 po q 12hr for 5 days. Eight of the 25 patients with acute nonlymphoblastic leukemia achieved a complete remission and 3 a partial remission. None of the five patients with acute lymphoblastic leukemia achieved a response and there was one partial remission in the seven patients with myelodysplastic syndrome or blastic CML. Reversible toxicity included nausea and vomiting (78%), alopecia (100%), pancytopenia (100%), mild stomatitis (63%), and hepatic dysfunction (24%). One patient developed seizures and cardiac arrhythmias. The activity of this combination in heavily treated patients with ANLL is comparable to that of the anthracycline-containing regimens, and its use in previously untreated patients with ANLL should now be explored. (Author abstract) (20 Refs)

26. COMBINATION CHEMOTHERAPY FOR MARROW RELAPSE IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOCYTIC LEUKAEMIA.

Amadori S, Spiriti MA, Meloni G, Pacilli L, Papa G, Mandelli F
Inst. Haematology, Univ. Rome, Via Chieti, 7, 00161 Rome, Italy
Scand J Haematol; 26(4):292-296 1981

Thirty-eight children with acute lymphocytic leukemia (ALL) in hematologic relapse were retreated with vincristine, daunomycin and prednisone (VPD) together with intrathecal methotrexate and prednisone, followed by asparaginase in those patients not in complete remission after 4 wk. The overall complete remission (CR) rate was 79%; asparaginase was needed to achieve CR in 7 of the 30 responding patients. The median duration of second remission was only 36 wk, but 6 out of 15 children receiving the COAP-POMP-CART consolidation regimen remain in continuous second remission after 37-260 wk; 3 of them are currently off all therapy. It is concluded that a prolonged second remission can be achieved in children with ALL in bone marrow relapse by combining intensive chemotherapy with the prevention of meningeal leukemia. (Author abstract) (14 Refs)

27. VINCRISTINE AND PREDNISOLONE INDUCTION AND REINFORCEMENT THERAPY FOR ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN.

Shetty PA, Antia FK, Jussawalla DJ
Dept. Chemotherapy, Tata Memorial Hosp., Parel, Bombay 400 012, India
Indian J Cancer; 18(2):150-152 1981

Twenty-five consecutive children (22 males, 3 females; aged 3-14 yr) with confirmed acute lymphoblastic leukemia were treated with induction therapy of vincristine (VCR: 1.4 mg/square meter iv/wk) until complete remission (CR) and prednisolone (PRN: 40 mg/square meter/day, po in divided doses administered concurrently). After induction of CR, cranial radiotherapy of 2,400 rads in 2.5 wk was administered together with intrathecal methotrexate (MTX: 10 mg/square meter 2x/wk x 5). Eighteen of the children were then randomized to receive 6-mercaptopurine (6-MP: 50 mg/square meter, po/day), MTX (10 mg/squar e meter/wk, po) as maintenance together with VCR and PRN as induction therapy; the other arm received maintenance therapy with 6-MP and MTX. Nineteen of the children achieved CR (remission rate 76%). Eighteen of the children were randomized soon after achieving CR: 9 in each arm of the study. Of the nine receiving reinforcement therapy along with maintenance, four relapsed and five continued in remission at 1 yr. Of the nine receiving maintenance therapy alone, seven relapsed and two continued in remission at 1 yr. (12 Refs)

28. TREATMENT OF ACUTE NONLYMPHOCYTIC LEUKEMIA BY CONCURRENT ADMINISTRATION OF N4-BEHENOYL-1-BETA-D-ARABINOFURANOSYLCYTOSINE, ACLACINOMYCIN A, 6-MERCAPTOPURINE AND PREDNISOLONE: A PILOT STUDY.

Hirano M, Morishita Y, Ino T, Matsui T, Shimizu S, Shigemura H, Nakamura K, Ono Y, Saito M
Dept. Medicine, Fujita-Gakuen Univ. Sch. Medicine, Toyoake, Aichi 470-11, Japan
Jpn J Clin Oncol; 11(1):87-92 1981

A pilot study on the effectiveness of aclacinomycin A (ACA) and N4-behenoyl-1-beta-D-arabinofuranosylcytosine (BH-AC) for the treatment of acute nonlymphocytic leukemia in eight patients (5 men, 3 women; 24-61 yr old) when used in combination with 6-mercaptopurine (6-MP) and prednisolone (PD). The treatment schedule consisted of daily administration of BH-AC (116-234 mg/square meter (m2) as a 2-hr iv infusion), ACA (12-16 mg/m2 as a 30-min iv infusion), plus 6-MP (100 mg/m2, po), and PD (40 mg/m2, po). Complete remission was obtained in six of the seven evaluable patients. One patient died of acute renal failure after one course of therapy. The median duration of complete remission was 5+ mo with a range of 4+ to 6 mo. Survival time of patients with complete remission ranged from 6+ to 27+ mo with a median of 9+ mo. Only one course of treatment was administered before complete remission occurred in all but one patient. Duration of treatment for each course was 6-14 days (median 10 days). The median dose of BH-AC administered per course was 1,491 mg/m2 and that of ACA was 132 mg/m2. Myelosuppressive and other side effects of the treatment are described. The results indicated that this regimen was quite effective as a remission inducer in acute nonlymphocytic leukemia of adults and deserves further study. (16 Refs)

29. THERAPY OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) USING ADRIAMYCIN (ADR) WITH OR WITHOUT HIGH DOSE ASPARAGINASE (ASP) (MEETING ABSTRACT).

Sallan SE
Sidney Farber Cancer Institute, Boston, MA
Pediatr Res; 15(4,Part2):587 1981

We initiated a protocol for non-T-cell childhood ALL that used q 3 weekly ADR. A random half of patients (pts) also received high dose ASP q 1 wk for 6 mo. All patients received cranial radiation and intrathecal methotrexate (MTX). After completing ADR, q 3 weekly pulses of MTX and 6-mercaptopurine were begun. Therapy was electively discontinued after the completion of 30 mo. Seventy-four pts entered remission between 1977 and 1979. After randomization there were two 36-pt groups: A) ADR without ASP; B) ADR with ASP. The groups were comparable in age and white blood count. However, Grp A had 11.13 patients whose lymphoblasts lacked the common ALL antigen. In Grp A 16/36 pts had failed compared to Grp B 9/36. The median time to failure for Grp A was 28 mo and disease-free survival in Grp B is 62%. The difference between the groups is not statistically significant, but the trend is apparent. Of the failures in Grp A, 15/16 relapsed; 11 in the bone marrow (BM) only, 1 in the CNS and 3 in the BM/CNS. Of the 9 Grp B failures 6 were relapses (3 BM, testicle, 2 CNS). Four children died in remission: 3 of adriamycin cardiomyopathy and 1 of sepsis. Efforts to decrease toxicity involve prediction of cardiac toxicity by the measurement of the myocardial contractile state (methoxamine stress testing) and

pharmacologic studies of ADR/ASP intractions. Further trials of therapy using high dose ASP for prolonged periods of treatment in childhood ALL appear warranted. (no Refs)

30. TREATMENT OF ADULT LYMPHOBLASTIC LEUKAEMIA USING CYCLICAL CHEMOTHERAPY WITH THREE COMBINATIONS OF FOUR DRUGS (COAP, POMP, TRAP SCHEDULE).

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Dept. Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, England

Postgrad Med J; 57(663):19-22 1981

Seventeen adult patients with previously untreated acute lymphoblastic leukemia (ALL) were entered into a schedule of chemotherapy in which three combinations, each of four drugs, were administered in a predetermined cyclical rotation in combination with cranial irradiation and intrathecal injections of methotrexate. Of the 17 patients, 16 completed induction therapy and 15 (94%) entered remission. The only patient with T-ALL died before receiving any therapy. The median survival for all patients (17) was 22 mo. Meningeal leukemia did not occur during the hematological remission phase although three patients developed this complication following relapse. The authors conclude that the addition of cyclophosphamide and cytosine arabinoside to vincristine/prednisone provides excellent remission induction but the aggressive maintenance schedule employed has not led to significant long-term survival. (Author abstract) (15 Refs)

31. TREATMENT OF REFRACTORY ADULT ACUTE LYMPHOCYTIC LEUKAEMIA AND ACUTE UNDIFFERENTIATED LEUKAEMIA WITH AN ANTHRACYCLINE ANTIBIOTIC AND CYTOSINE ARABINOSIDE.

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Dept. Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

Br J Haematol; 48(3):369-375 1981

Ten patients with acute lymphocytic leukemia (ALL) and 4 patients with acute und ifferentiated leukemia (AUL) in relapse or refractory to conventional therapy were treated with remission induction therapy consisting of an anthracycline antibiotic and cytosine arabinoside. Twelve patients had previously demonstrated resistance to vincristine-prednisone and 9 patients had prior anthracycline therapy. Nine patients achieved complete remission after one course of therapy with a median time to remission of 30 days. Of five nonresponders, three died of sepsis with marrow hypocellularity and no evidence of residual leukemia. Only two patients had unequivocal evidence for resistance to an anthracycline-cytosine arabinoside regimen. Myelosuppression and infection were the most significant complications of therapy. The data presented indicate that marrow ablative chemotherapy with an anthracycline antibiotics and cytosine arabinoside is an effective regimen for remission induction in adults with ALL and AUL refractory to vincristine-prednisone. The use of these agents in remission consolidation therapy may offer the possibility of providing a reduction in residual resistant cells that are present after successful remission induction therapy with conventional agents. (Author abstract) (24 Refs)

32. TREATMENT OF ACUTE NONLYMPHOBLASTIC LEUKEMIA.

Paul C, Bjorkholm M, Christenson I, Engstedt L, Gabrton G, Hast R, Holm G, Killander A, Lantz B, Lockner D, Loennqvist B, Mellsted H, Palmblad J, Peterson C, Simonsson B, Stalfelt AM, Uden AM, Wadman B

Dept. Medicine, Huddinge Hosp., S-141 86 Huddinge, Sweden

Cancer Chemother Pharmacol; 6(1):65-73 1981

The results of a random study performed to evaluate the efficacy of daunorubicin (DNR) and the daunorubicin-DNA complex (DNR-DNA) in the treatment of 60 patients (15-60 yr old) with acute nonlymphoblast . leukemia are described. Patients were divided into three treatment groups: R1, DNR (1.5 mg/kg, push) on day 1 and cytarabine (ARA-C: 1 mg/kg, iv, bid) on days 1-5; R2, DNR (1.5 mg/kg as a 4-hr infusion) on days 1 and 2, day three drug-free, ARA-C (1 mg/kg, iv, bid) twice daily on days 4-8, days 9-16 drug-free; and R3, identical to R2 except that DNR-DNA was given at a rate of 100 ml/hr instead of DNR. Regimens were repeated until remission was obtained. A complete remission was induced in 14/20 patients with R1, 13/18 with R2, and 15/22 with R3. Compliance with the program was mainly good, although five patients (two receiving R1, one R2, and two R3) required additional cytostatic treatment before they achieved complete remission. There was a tendency to a larger number of induction courses with R1 than with R2 and R3, but the dose of DNR needed for a complete remission was somewhat lower with R1 than with R2 and R3. Older patients showed a tendency to have a lower remission rate only in the R2 group. The causes of death in patients wit hout remission are presented. The median duration of the first remission was 300 days in R1, 335 days in R2, and 295 days in R3. The median survival time for all patients was 270 days in R1, 420 days in R2, and 540 days in R3. In 16 patients cardiac abnormalities appeared that could be related to DNR treatment. Cardiotoxicity was most evident in the R2 group and least evident in the DNR-DNA group. The most pronounced drop in platelet count was in the R2 group. Other toxic effects of DNR treatment are described. (31 Refs)

33. EFFECT OF ACNU (NSC D245382) ON CHRONIC MYELOCYTIC LEUKEMIA.

Takubo T, Namiuchi S, Ueda T, Shibata H, Nakamura H, Masaoka T, Yoshitake J, Ishigami S

Center for Adult Diseases, Osaka, Higashinari-ku, Osaka 537, Japan

Gan To Kagaku Ryoho; 8(2):290-292 1981

During the Phase-II study, the effectiveness of 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea (ACNU) on chronic myelocytic leukemia (CML) was studied in 21 cases, of which 10 were previously untreated and 11 were treated with busulfan. Patients were given ACNU (2 mg/kg) iv by drip infusion once a wk or every 2 wk for 2 to 11x. A decrease of WBC was observed in all 21 cases. This decrease began in the 1st wk and reached a nadir in the 5th or 6th wk after administration of ACNU. WBC decreased in mean value from an initial 105,400 to 22,600/cmm, and platelets decreased from 659.6 x 10(3) to 396.5 x 10(3)/cmm. The decrease in platelet count was relatively less than that of the WBC count. However, in some cases a rapid decrease of platelet count was noted. On the other hand, the effect of ACNU on the red cells was slight. Regression of splenomegaly was observed in 11 out of 15 patients, and disappeared in 5 out of 15 patients. With ACNU treatment, remission was achieved in 11 out of 21 patients and the mean duration of remission was 2.6 mo. In some cases remission after ACNU treatment of 2 to 4 doses of the drug has lasted for more than 6 mo without any

maintenance therapy. The most conspicuous characteristic of ACNU action on CML is the long duration of remission. The main side effect by ACNU was nausea. ACNU can be used easily for out-patients, since the frequency of administration of the drug is once a wk or less. Clinically no resistance to other drugs, including busulfan, was observed. ACNU seems very promising for the treatment o CML. (Author abstract) (11 Refs) (In JPN)

34. CLINICAL PHARMACOLOGY OF ORAL THIOGUANINE IN ACUTE MYELOGENOUS LEUKEMIA.

Brox LW, Birkett L, Belch A
McEachern Lab., Univ. Alberta, Edmonton, T6G 2H7, Canada
Cancer Chemother Pharmacol; 6(1):35-38 1981

High performance liquid chromatogrhy was used to examined the plasma levels of thioguanine (TG) administered po to 13 adult patients with acute myeloblastic leukemia either during remission induction with daunomycin, cytarabine, and TG or during maintenance therapy with cytarabine and TG. The peak plasma levels ranged from 0.03-0.84 uM with the time to peak levels being about 4 hr when food was given or about 1.5 hr with no food. This trend was not statistically significant. In 4/5 instances higher peak levels were observed when the drug was given to a fasting patient. The 12-hr carryover plasma level of TG was very low except in one instance, where a prolonged time of drug absorption was observed. The lowest plasma levels of TG were observed in patients who were severely nauseated and who vomited 60-90 min after drug administration. There was no relationship in this study between the peak plasma levels obtained and the number of cycles of chemotherapy the patient had undergone, or between drug level and WBC count. The plasma disappearance curves for TG showed a rapid decrease after the peak level was attained, followed by a gradual decrease. The av plasma TG half-life for the initial rapid decrease was 110 min, with a range between 45 and 240 min. The results indicated the erratic oral absorption of TG and the frequently low peak plasma levels. In view of these findings, it was suggested that the iv formulation of TG may be superior to the same drug given po. (8 Refs)

35. CARDIOTOXICITY OF ANTHRACYCLINE ANTIBIOTIC IN CHILDHOOD LEUKEMIA AND OTHER MALIGNANCIES.

Azuma E, Ido M, Hirai S, Suzuki M, Arai S, Nakano C, Komada M, Komada Y, Iguchi K, Hirota H, Nobori T, Kamiya H
Dept. Pediatrics, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):305-310 1981

Fifty-four patients (30 boys, 24 girls; aged 0-18 yr) with leukemia (34 cases), malignant lymphoma (4), osteosarcoma (3), neuroblastoma (8), Ewing's sarcoma (2), and one each with malignant reticulosis, Wilms' tumor, and pontine glioma, were treated with anthracycline antibiotics. The agents employed included doxorubicin, daunorubicin and cytosine arabinoside combined with other antineoplastic drugs. The chronic cumulative cardiotoxicity of these drugs was studied with regard to dose, duration of administration, and duration of remission. Abnormal findings in chest roentgenograms (X-p), electrocardiogram (ECG), and echocardiogram (UCG) were used to measure cardiac function. Eight patients developed abnormalities in two or more of these parameters. Seven of these patients did not achieve complete remission or developed frequent relapses, with a cumulative dose ranging from 175-840 mg/square meter (m2) (mean dose: 535 mg/m2). The eighth case was a 13-yr-old girl with acute promyelocytic leukemia who achieved complete remission after two courses of induction therapy and maintenance therapy every 3 mo, for a total cumulative dose of 738 mg/m2. The girl was markedly obese and wt gain was remarkable after admission. The increased car diac load due to obesity may be a precipitating factor of anthracycline cardiotoxicity. In patients in complete remission who show abnormalities in chest X-p, ECG and/or UCG, the administration of anthracycline antibiotics should be discontinued. (15 Refs)

36. SMALL BOWEL ENTEROCYTE ABNORMALITIES CAUSED BY METHOTREXATE TREATMENT IN ACUTE LYMPHOBLASTIC LEUKAEMIA OF CHILDHOOD.

Gwavava NJ, Pinkerton CR, Glasgow JF, Sloan JM, Bridges JM
(c/o Pinkerton) Dept. Child Health, Inst. Clinical Science, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland
J Clin Pathol; 34(7):790-795 1981

Jejunal biopsy specimens from 10 children with acute lymphoblastic leukemia on methotrexate treatment were compared with 10 from children being investigated for diarrhea or failure to thrive. In association with methotrexate treatment on both light and electron microscopy, there were marked morphological abnormalities in the villus enterocytes. These consisted of a striking distention of the lateral basal intercellular spaces, cell vacuolation and patchy necrosis and was most marked when methotrexate treatment was given between 24 and 72 hr before biopsy. Two mechanisms may be involved: an early direct toxic effect on the mature enterocyte coupled with interference with crypt cell generation, possibly causing ageing and loss of cells proximal to the normal extrusion zone. These pathological changes may account for the malabsorption in association with methotrexate treatment. (Author abstract) (25 Refs)

SUPPORTIVE CARE

37. A CONTROLLED TRIAL OF PROPHYLACTIC GRANULOCYTE TRANSFUSIONS DURING INITIAL INDUCTION CHEMOTHERAPY FOR ACUTE MYELOGENOUS LEUKEMIA.

Strauss RG, Connett JE, Gale RP, Bloomfield CD, Herzig GP, McCullough J, Maguire LC, Winston DJ, Ho W, Stump DC, Miller WV, Koepke JA
Dept. Pediatrics, Univ. Iowa, Iowa City, IA, 52242
N Engl J Med; 305(11):597-603 1981

Whether daily prophylactic granulocyte transfusions would reduce the rate of bacterial infections in patients with acute leukemia undergoing initial remission-induction chemotherapy was investigated in 102 patients (54 males, 48 females; mean age 48.8 yr; 62 with acute myelocytic leukemia, 3 with promyelocytic, 10 with monoblastic, 19 with monomyeloblastic, and 8 other leukemias). Fifty-four patients received granulocyte transfusions with a median daily dose of 3.4 x 10(9)/square meter, a median number of transfusions of 18.5, and a median dose per course of 67.2 x 10(9)/square meter. Forty-eight patients did not receive such transfusions and served as controls. Daily prophylactic granulocyte transfusion was of no benefit to the overall incidence of infections, recovery of marrow function, complete remission rate, mortality during induction chemotherapy, duration of first remission, or survival. Of the 987 transfusions that were given, adverse side effects accompanied 158 (16%). The incidence of pulmonary infiltrates was strikingly higher in the transfusion group than the controls (31/54, 57% vs 13/48, 27%, respectively), and and 35% of pa-

tients in whom pulmonary infiltrates developed died during the study, compared with 5% without infiltrates. These data and a review of the literature indicate that prophylactic granulocyte transfusions cannot be recommended as routine therapy during initial remission-induction chemotherapy in patients with acute myelogenous leukemia. (22 Refs)

38. INFUSION OF CRYOPRESERVED AUTOLOGOUS MARROW IN THE TREATMENT OF ACUTE LEUKEMIA: A PRELIMINARY REPORT.

Harada M, Ishino C, Yoshida T, Matsue K, Nakamura S, Hattori K
Dept. Medicine, Kanazawa Univ. Sch. Medicine, Kanazawa 920, Japan
Jpn J Clin Oncol; 11(1):81-86 1981

Clinical trials of autologous infusion using cryopreserved remission marrow were performed to determined the hematopoietic activity of frozen-thawed marrow and its therapeutic effect in the treatment of patients with acute leukemia. Three patients with acute myelogenous leukemia (AML) and one with acute lymphoblastic leukemia (ALL) took part in the study. The total number of nucleated marrow cells varied from case to case. No relationship between vol and number of cells obtained was seen. Similarly, the number of myeloid progenitor cells recovered varied. All patients achieved their second remission within 2 wk after autologous marrow infusion. Despite high-dose chemotherapy, hematologic recovery from the drug-induced bone marrow depression was not delayed. In two patients with AML, the hematologic recovery was observed 1-2 wk earlier with autologous marrow infusion than the recovery leading to the first complete remission obtained by chemotherapy alone. There appeared to be no correlation between the time of hematologic recovery and the marrow dose. The results indicated that cryopreserved autologous marrow may retain its hematopoietic activity and autologous marrow infusion may be effective in providing early recovery or rescue from bone marrow failure. (10 Refs)

39. TRANSPLANTATION FOR ACUTE LEUKAEMIA WITH HLA-A AND B NONIDENTICAL PARENTAL MARROW CELLS FRACTIONATED WITH SOYBEAN AGGLUTININ AND SHEEP RED BLOOD CELLS.

Reisner Y, Kirkpatrick D, Dupont B, Kapoor N, Pollack MS, Good RA, O'Reilly RJ
Memorial Sloan-Kettering Cancer Center, Box 380, 1275 York Ave., New York, NY, 10021
Lancet; 2(8242):327-331 1981

A new procedure for enrichment of marrow precursors and removal of T lymphocytes from large vol of human bone marrow, involving initial differential agglutination of T lymphocytes and mature marrow elements with soybean agglutinin, followed by rosetting with sheep RBCs, was used to fractionate marrow cells from an HLA-A, B, DR non-identical, MLC non-reactive, paternal donor for transplantation into an infa nt with acute leukemia. This transplant became completely engrafted and resulted in full recovery of normal, donor-derived hematopoietic function without graft-versus-host disease, sustained for 11 wk after transplantation, at which time the patient's leukemia recurred. Subsequently, the patient received chemotherapy and achieved a remission with regeneration of normal marrow cells of donor origin. The patient's course demonstrated the potential of lectin-separated marrow grafts to restore durable hematopoiesis, without graft-versus-host disease, in a lethally irradiated allogeneic host. (Author abstract) (23 Refs)

40. EFFECTIVENESS OF LAMINAR AIR FLOW FOR THE TREATMENT OF ACUTE LEUKEMIA.

Namiuchi S, Kubota Y, Takubo T, Ueda T, Nakamura H, Shibata H, Masaoka T
Dept. Medicine, Center for Adult Diseases, Osaka, Japan
Rinsho Ketsueki; 22(4):444-451 1981

Incidences of infection in 47 patients (41 men, 6 women; 21-63 yr old) with acute leukemia were studied to determine the effectiveness of laminar air flow (LAF) rooms in reducing infection. Of the 47 patients, 20 had acute myeloblastic leukemia, 10 had acute monocytic leukemia, 2 had acute promyelocytic leukemia, 9 had acute lymphoblastic leukemia, 1 had erythroleukemia, and 5 had chronic myelogenous leukemia with blast crisis. LAF rooms were used during induction therapy in 21 patients, and conventional (C) hospital rooms were used during the induction therapy of 26. Both groups of patients received the same routine nursing care. The incidences of fever, infections, and bacterial inflammations occurred less often in the patients treated in the LAF rooms than in those in the C rooms. Pneumonia was not observed in any of the LAF room patients, but it was observed in 14% of the C room patients. The results indicated that LAF rooms reduced incidence of infections in spite of very simple nursing procedures. However, prophylactic measures were recommended to prevent septicemia and control internal microbes. (15 Refs) (In JPN)

SELECTED PRE-CLINICAL STUDIES

41. IMMUNOTHERAPY OF MURINE LEUKEMIAS BY MONOCLONAL ANTIBODY. I. EFFECT OF PASSIVELY ADMINISTERED ANTIBODY ON GROWTH OF TRANSPLANTED TUMOR CELLS.

Eirch ME, Hemmerling U
Dept. Immunochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Immunol; 127(2):805-810 1981

The objective of the present study was to establish a model system for the evaluation of passive immunotherapy of murine leukemias. Monoclonal antibodies directed at T lymphocyte differentiation antigens (Thy 1 and Lyt 2) were tested for their effect on tumors that were grown in hosts congenic for the target antigen. Tumor challenges were selected that were at least 500 x the dose that was lethal in 50% of untreated controls. The A strain leukemia, ASL.1, was transplanted sc into A/Thy 1.1 conge nic hosts. Ip administration of anti-Thy 1.2 monoclonal antibodies of the IgG3 and IgM classes reduced tumor growth. Up to 90% of the mice receiving antibody of the IgG3 subclass failed to develop tumors, whereas IgM antibodies prolonged survival time, but the mice eventually died of tumors. Antibody was most effective if administered within 24 hr of tumor inoculation; delay of antibody injection for 48 hr prolonged host survival but did not eradicate cells at the injection site or prevent metastases. The C57BL/6-derived tumors, ERLD and EL4, were evaluated for susceptibility to treatment with antibody directed at the Lyt 2.2 alloantigen using the protocol that was effective in treating ASL.1. Monoclonal antibody of the IgG2a subclass was effective in the case of C57BL/6/Lyt 2.1 congenic mice bearing ERLD, but caused a decrease in survival time of mice bearing the transplanted EL4 tumor. Thus, antibody of the appropriate immunoglobulin subclass can be effective in controlling tumor growth if administered in the optimal treatment regimen, but inherent features of

the tumor cell ultimately determine whether abrogation or enhancement of growth will occur. (Author abstract) (47 Refs)

42. COMPARATIVE CHEMOTHERAPEUTIC INVESTIGATIONS ON TRANSPLANTED AND AUTOCHTHONOUS ACUTE RAT LEUKEMIAS.

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J Cancer Res Clin Oncol; 160(3):239-246 1981

The effect of a clinically established drug combination (vincristine, adriamycin, and cytosine arabinoside) against the transplanted rat leukemia L5222 originally induced by ethylnitrosourea (ENU) was compared with its effect against autochthonous acute rat leukemias, also induced by ENU. BD IX rats were used for the transplantation studies and Wistar rats for the autochthonous leukemia studies. Four initial therapy cycles of the drugs was given to compare the response of both leukemia models. In the transplanted model, four cycles had to be given without interruption, and it was impossible to achieve a remission, despite a median survival time of 33 days corresponding to 230% increase in median life-spans of treated rats over that of untreated controls (ILS). The median survival time of the treated autochthonous leukemias for 70 days, corresponding to 419% ILS. For all 15 treated autochthonous leukemias, complete remission was achieved with a median duration of 43 days. The difference in response of these leukemia models is attributed to differences in their kinetics. It is suggested that autochthonous rat leukemias are considerably closer to the human situation than the transplanted rat leukemias. (8 Refs)

43. EFFICACY OF PIPERAZINEDIONE PRIOR TO BONE MARROW TRANSPLANTATION: STUDIES IN A RAT MODEL FOR HUMAN ACUTE MYELOCYTIC LEUKEMIA.

Hagenbeek A, Martens AC

Transplantation Biology Unit, Univ. California Los Angeles Sch. Medicine, Center Health Sciences, Los Angeles, CA, 90024

Cancer Treat Rep; 65(7/8):575-582 1981

The efficacy and toxicity of piperazinedione were investigated in a Brown Norway rat model for acute myelocytic leukemia (BNML). Treatment was started at a stage which is comparable to a 'full-blown' relapse in human patients. Early toxicity-induced deaths due to the very strong myelosuppressive effect of the drug could be prevented by bone marrow transplantation followed by repeated blood transfusions. However, with a total dose of 16 mg/kg (human dose, 85 mg/m(2)), death caused by GI tract and lung damage was inevitable. As judged by prolongation of survival, at the most a 9-log cell-kill was achieved. No cures were obtained, since the tumor load at the start of treatment was greater than 10(9) cells (about 5 x 10(9)). The possible presence of drug-resistant cells was not excluded. No significant differences in efficacy were found between daily 'push' treatment and split daily doses using total doses of 10-12 mg/kg. (Author abstract) (17 Refs)

44. AN EXPERIMENTAL APPROACH TO LEUKAEMIC CARDIOMYOPATHY: EFFECTS OF LEUKAEMIC BLAST CELL EXTRACT ON ULTRASTRUCTURAL CHANGES AND MITOCHONDRIAL RESPIRATION OF RAT HEART (MEETING ABSTRACT).

Mir MA, Charalambous BM, Nicholas N

Department of Medicine, University Hospital of Wales, Heath Park, Cardiff, Wales

Clin Sci; 60(3):28P 1981

We have put forward a hypothesis which suggests that leukemic blast cells contain a cardiotoxic substance which predisposes leukemic hearts to daunorubican toxicity. In an effort to test this hypothesis we injected intraperitoneally blast cell extract (BCE), 0.1 ml (10 ug of protein), and WBC extract (as control) on days 1, 2 and 3 to neonatal rats, which were killed after 12 wk. The heart/body wt ratios of BCE treated rats were lower than those in control rats. Most pronounced ultrastructural changes were seen in mitochondria, which were packed with bent, angulated and whirled cristae. The muscle fibers were disorganized mostly in Z-band areas. To elucidate further the effects of BCE on mitochondria, we isolated mitochondria from normal rats and studied the effects of BCE and WBC extract (WCE) on mitochondrial respiration. BCE (5 ug in 3 ml of mitochondrial suspension) showed a significantly higher rate of oxygen consumption, higher respiratory control index, and higher ADP/O ration than WCE. This increased mitochondrial respiration presumably leads to angulated and whirled formation of the cristae seen in adult rats exposed to BCE at the neonatal stage. The simulatory effect on mitochondria may be caused by inadequate utilization or delivery of ATP to the contractile apparatus of the muscle. These studies suggest that BCE interferes w ith myocardial metabolism and predisposes the leukemic hearts daunorubicin toxicity. (no Refs)

REVIEWS

45. THE SELECTIVE USE OF CYTOCHEMISTRY AND SURFACE MARKERS FOR THE DIAGNOSIS OF LEUKEMIAS AND LYMPHOMAS--A PRACTICAL APPROACH.

Sun T

Dept. Pathology, Cornell Univ. Medical Coll., New York, NY

Lab Med; 12(7):424-431 1981

Most leukemias and lymphomas can be identified by a few cytochemical tests: myeloperoxidase (positive in myeloid leukemias), chloroacetate esterase (specific esterase; positive in myelocytes), alpha-naphthyl butyrate esterase (nonspecific esterase; diffusely positive in monocytes, focally positive in T-lymphocytes), E-rosetting (T-cells), and several immunoglobulin (Ig) antisera. Other tests include PAS staining, assays for acid phosphatase, terminal deoxynucleotidyl transferase (TdT), leukocyte alkaline phosphatase, lysozyme, cytoplasmic Ig, Fc and complement receptors, and binding to mouse RBC (MRBC) the total B-cell count and the ratio of different classes of surface light and heavy chains distinguishes between benign and malignant lymphoproliferative diseases. The presence of a monoclonal surface Ig on 75% or more of the B-cells indicates a malignant lymphoma. If the surface Ig is polyclonal, a neoplasm cannot be definitely excluded but a benign condition is more probable. A markedly elevated number of phagocytic cells suggests a monocytic or histiocytic neoplasm. Other

markers associated with malignancy include selective depletion of normal markers, the coexistence of multiple markers that normally are not present in combination (eg, T-cell and B-cell markers on the same cells), markers for immature cells (cytoplasmic Ig in non-plasma cells, also TdT), and rosette formation with MRBC. The use of polyvalent Ig antisera and monospecific antisera against IgG, IgM, IgA, IgD, and the kappa and lambda chains is sufficient to identify most lymphomas and lymphoid leukemias. (28 Refs)

46. A CLINICAL STUDY OF LEUKEMIA IN THE ELDERLY: AN APPROACH TO THE ESTABLISHMENT OF ITS CLASSIFICATION AND TREATMENT.

Wada H
Dept. Geriatric Medicine, Tokyo Medical Coll., Shinjuku-ku, Tokyo 160, Japan
Tokyo Ika Daigaku Zasshi; 39(1):117-134 1981

The incidence of leukemia in the elderly has been increasing recently. Unlike leukemia in adolescence and middle age, leukemia in old age is frequently atypical and refractory, and its clinical behavior is obscure. To clarify its clinical behavior and evaluate its treatment from the geriatric standpoint, the clinical behavior, classification, prognosis and treatment of 61 patients with leukemia over 60 yr of age encountered in the Tokyo Medical College Hospital in the past 16 yr were investigated, with specific selection of typical and atypical cases of acute myelogenous leukemia (AML) for a comparative study. In atypical cases, clinical symptoms were few, and pancytopenia was frequently found at the first examination. The median survival time was 11.25 mo for AML (5.5 mo for typical cases, and 17 mo for atypical cases). The survival time was 4.6 mo for patients treated with a single agent, 7.7 mo for those treated with two agents, and 7.9 mo for those treated with multiple agents among typical cases, while it was 18.7 mo in the single-agent group and 6.7 mo in the two-agent group among atypical cases. The survival time after initiation of chemotherapy, however, was shortened to 6.2 mo in the single-agent group, and 1.5 mo in the two-agent group among atypical cases. In typical cases, the lower was the platelet count at the first examination, the more unfavorable was the prognosis. As for complications, infections developed in both typical and atypical cases, but hemorrhage was predominantly in the digestive tract in typical cases and in the brain in atypical cases. (32 Refs) (In JPN)

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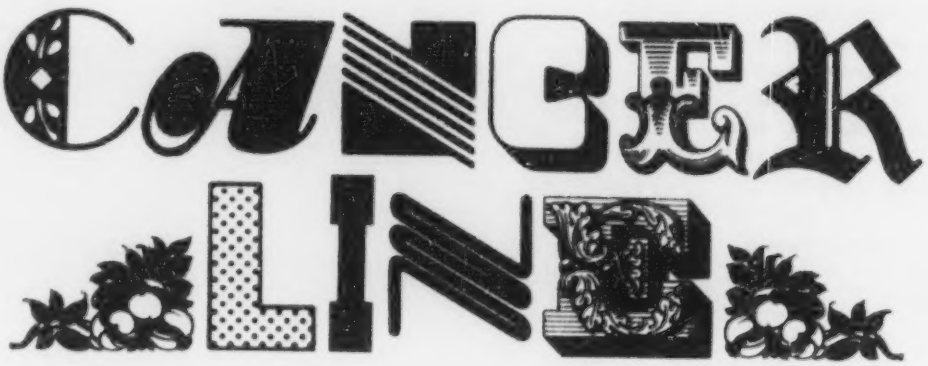

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Diagnosis, Treatment

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DIAGNOSIS

1. X-RAY MANIFESTATION OF THE CHEST IN ACUTE LEUKEMIA OF CHILDREN.

Li G, Wei D
People's Hosp., Guangdong Province, People's Republic of China
Zhonghua Fangshexue Zazhi; 15(1):25-28 1981

Radiologic manifestations of the chest are described for 49 cases (32 males, 17 females; aged 1-13 yr) that consisted of 37 cases of acute lymphocytic leukemia, 10 cases of acute granulocytic leukemia and 2 cases of acute monocytic leukemia. Abnormal findings were observed in 71.4% (35/49) of this series. The abnormal changes were found mostly in the lungs (27 cases) and mediastinal lymph nodes (19 cases) of acute lympho-

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cytic and acute granulocytic leukemia patients. The two cases of acute monocytic leuke mia showed no abnormal x-ray changes. Chest x-ray changes as a result of pathologic changes in acute leukemia are discussed. (7 Refs) (In CHI)

2. CENTRAL NERVOUS SYSTEM LEUKEMIA AND LYMPHOMA: COMPUTED TOMOGRAPHIC MANIFESTATIONS.

Pagani JJ, Libshitz HI, Wallace S, Hayman LA

Dept. Diagnostic Radiology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner, Houston, TX, 77030

AJNR; 2(5):397-403 1981

Experience with the intracranial computed tomographic (CT) manifestations of leukemic and lymphomatous masses in 405 patients (245 with leukemia, 148 systemic non-Hodgkin's lymphoma, 12 systemic Hodgkin's lymphoma) is reviewed. After contrast enhancement, 31 patients had intracerebral lesions; the CT abnormalities in these patients were correlated with the underlying malignancy, cerebrospinal fluid cytology, and treatment. All CT studies were performed with an EMI 1010 scanner either immediately after 40 g iv iodine or 1 hr after high dose (80 g iodine) contrast infusion. Abnormalities in 24/245 patients with leukemia included leukemic masses (8), hemorrhage (9), abscesse (2) , and 5 other abnormalities including one each acoustic neuroma, astrocytoma, and methotrexate leukoencephalopathy. The only CT abnormality in 160 lymphoma patients was a tumor mass in 7. CT was normal in 374 patients including 148 with meningeal disease diagnosed by cerebrospinal fluid cytologic examination. Malignant masses before treatment appeared isodense or of greater density with varying amounts of edema. Worsening was indicated by increase in the size or number of masses. After radiation therapy and chemotherapy, a central low density region with an enhancing rim developed. The differential diagnosis of the various abnormalities is discussed. (24 Refs)

3. PRETREATMENT TESTICULAR BIOPSY IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKAEMIA.

Kim TH, Brynes RK, Lui VK, Hargreaves HK, Hawkins HK, Woodard J, Ragab AH

Dept. Pediatrics, Emory Univ. Clinic, 1365 Clifon Road, Atlanta, GA, 30322

Lancet; 2(8248):657-658 1981

Between August, 1978, and March, 1981, 24 boys with acute lymphocytic leukemia (ALL) (14 non-B-cell non-T-cell, 6 pre-B-cell, and 4 T-cell) underwent bilateral wedge testicular biopsy at initial diagnosis. All testes were of normal size. Histological analysis was performed independently by three pathologists, 4 (3 non-B non-T, and 1 pre-B) of 20 patients with non-T-cell ALL demonstrated testicular focal lymphoblastic involvement. Successful induction chemotherapy without concomitant testicular irradiation completely eradicated testicular infiltrates in all four patients. Only one of the four T-cell patients had pre-treatment testicular infiltrates. Unlike boys with non-B non-T leukemia, attainment of bone-marrow remission in this patient was associated with persistent testicular disease. The se preliminary data indicate that in patients with ALL of non-T cell type, systemic induction chemotherapy eradicates the small testicular infiltrates of lymphoblasts. Prophylactic testicular irradiation in this group of patients does not seem to be warranted. (Author abstract) (10 Refs)

4. CYTOCHEMICAL CHARACTERISTICS AND IMMUNOLOGIC MARKERS IN ACUTE LYMPHOBLASTIC LEUKEMIAS.

Dorlhiac P, Genter G, Jamra M

(c/o Jamra) Fundacao Maria Cecilia Souto Vidigal, Instituto de Hematologia, Rua Pedroso de Alvarenga, 1255 - 1 andar, 04531 Sao Paulo, Brazil

Sangre (Barc); 26(4):433-438 1981

Seventeen acute lymphoblastic leukemia patients were studied. 23.5% were classified as being of T cell type, 70.5% of Null cell type and 6% of B cell type. Fifty percent of the T cell leukemias presented with mediastinal masses and total WBC count in the peripheral blood of more than 100,000 per mm3. The cytochemical and acid phosphatase reaction showed typical unipolar positivity in 50% of the T cell leukemias. Other cytochemical reactions, as PAS and ANAE were not able to identify the different immunologic types of acute lymphoblastic leukemias. On the other hand no correlation between the immunologic markers and the cytologic features according to the F.A.B. classification, was observed. This study shows that the behavior of our acute lymphoblastic leukemia cases is similar to that described in other areas. (Author abstract) (24 Refs) (In SPA)

5. SCANNING IMMUNO-ELECTRON MICROSCOPY OF HUMAN LEUKAEMIA AND LYMPHOMA CELLS: A COMPARATIVE STUDY OF TECHNIQUES USING IMMUNOLATEX SPHERES AS MARKERS.

Gamliel H, Leizerowitz R, Gurfel D, Polliack A

Dept. Hematology, Hadassah Univ. Hosp., Jerusalem, Isreal

J Microsc; 123(2):189-199 1981

Scanning immuno-electron microscopic (SIEM) techniques were used to identify human leukemia-lymphoma cells, using monodispersed polystyrene (latex) beads conjugated to specific antisera by glutaraldehyde (immunolatex spheres). A variety of cells of known origin were studied in an attempt to detect surface antigenic components. The antisera were usually immunoglobulin fractions and were prepared against human thymus-derived (T) cells, common type acute lymphoblastic leukemia (C/ALL) cells, and surface immunoglobulin (sIgG)-bearing cells. Several types of experiments were carried out: (1) to determine whether it is essential to neutralize fixed samples with glycine before the addition of immunolatex, (2) to test the immunospecificity of the antisera conjugated to the latex spheres, using both fixed and unfixed cells, and (3) to ascertain the surface morphology of human leukemia-lymphoma cells positively labeled with the specific antisera. Glycine treatment was essential for detecting specific antigenic sites on the cell surface by SIEM. The immunospecificity of the heteroantisera was adequate; insignificant n on-specific attachment and cross reactivity were seen. SIEM is a useful technique for ultrastructural studies of the human leukemia-lymphoma cells and is a potentially useful tool in their identification. (32 Refs)

6. ULTRASTRUCTURAL STUDY OF CHRONIC MYELOID LEUKEMIA IN BLAST CRISIS USING MYELOPEROXIDASE AND ACID PHOSPHATASE REACTIONS.

Soligo D, Lambertenghi-Deliliers G, Pozzoli E, Nava M, Polli N, Maiolo AT
(c/o Lambertenghi-Deliliers), Istituto di Clinica Medica I, via F. Sforza, 35, 20122 Milano, Italy
Haematologica (Pavia); 66(2):141-150 1981

Ten patients with chronic myeloid leukemia (CML) in blast crisis (BC) were studied with ultrastructural cytochemical methods after myeloperoxidase (MP) and acid phosphatase (AP) reactions. In four cases, the diagnosis by light microscopy was of BC of the myeloid type; both bone marrow and peripheral blood smears showed a high percentage (greater than 80%) of granular blasts, Sudan black B and peroxidase positive, PAS negative, and specific esterases weakly positive. This diagnosis was confirmed by electron microscopy. The peripheral blasts presented the ultrastructural characteristics of myeloblasts and/or promyelocytes and there was an intensely positive reaction to peroxidase both in the granulation and the endoplasmic reticulum or perinuclear cisterna. Some granules showed a poorly condensed matrix, while irregularly shaped membrane-bound structures containing a flocculent peroxidase-positive material were frequently observed. In two cases tested, 50% of the granular blasts were AP-positive. Classification of six cases was not possible using the light microscope; both bone marrow and peripheral blood smears showed a high percentage (greater than 80%) of agranular blasts always negative with cytochemical reactions. The electron microscopic characteristics of these cells are described. The MP reaction was constantly negative in these cells and also in the membranous system. In 3/6 of these cases, the AP reaction was positive in 20-30% of the blasts. The results indicated that ultrastructural study of agranular cells present in BC of CML could provide additional morphological data. (20 Refs)

7. CHROMOSOME STUDIES IN ADULT T-CELL LEUKEMIA IN JAPAN: SIGNIFICANCE OF TRISOMY 7.

Ueshima Y, Fukuhara S, Hattori T, Uchiyama T, Takatsuki K, Uchino H
Dept. Medicine, Box 420, Univ. Chicago, Chicago, IL, 60637
Blood; 58(3):420-425 1981

Chromosomes were studied in cells from 15 Japanese patients with adult T-cell leukemia (ATL). Mitoses were obtained from unstimulated peripheral blood in 12 patients and a lymph node in 1 patient. In two other patients, mitotic cells were obtained solely from peripheral blood stimulated with phytohemagglutinin (PHA). Chromosomally abnormal cells were seen in 14 of the 15 patients. The abnormal cells had a modal number of chromosomes in near diploid range in 12 patients, and in near triploid and tetraploid range in the remaining 2 patients, respectively. Eight of the nine patients analyzed by Q-banding had clonal chromosome abnormalities. The most common abnormality was trisomy number 7 or 7q, which was seen in five cases and has been primarily observed in lymphoid neoplasms. A 14q+ marker chromosome was found in two patients and a Dq+ in one patient; loss of a sex chromosome was found in three patients. Most chromosomes were involved in gains, losses, or structural rearrangements, but abnormalities of number 11, which have been frequently found in lymphoid malignancies, was not observed in our series. The significance of these chromosome abnormalities is discussed. (Author abstract) (37 Refs)

8. DIFFERENTIAL DIAGNOSTIC SIGNIFICANCE OF ACID PHOSPHATASE AND BETA-GLUCURONIDASE CYTOCHEMICAL TESTS IN ACUTE LEUKEMIAS.

Telek B, Kiss A, Pecze K, Jako J, Rak K
II. Belgyogyaszati Klinika, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Orv Hetil; 122(27):1631-1633 1981

The significance of the cytochemical determination of the acid phosphatase (AP) and beta-glucuronidase (BG) activities in the differential diagnosis of acute leukemias was studied in bone marrow smears from 52 adult patients. Acute myeloid leukemia was diagnosed in 19 cases, acute myelomonocytic leukemia in 12, acute monocytic leukemia in 3, acute lymphocytic leukemia (ALL) in 5, T-cell ALL in 3, and non-B non-T ALL in 10. The BG test was negative in 8/52 cases, diffuse positive in 21, diffuse-granular in 9, and granular in diffuse-granular in 6 granular cytoplasmic in 6, and perinuclear in 2. Both tests were positive (diffuse or diffuse-granular) in all 34 patients with acute nonlymphocytic leukemias, and the intense diffuse positivity of AP was suggestive of monocytic leukemia. In the positive cases of ALL, both the AP and BG were of granular character. The AP activity was frequently increased in the patients with T-cell ALL, and the BG activity was frequently increased in those with non-B non-T ALL. (29 Refs) (In HUN)

9. SERUM IMMUNE PROTEINS AND ACID PHOSPHATASE ACTIVITY OF LYMPHOCYTES IN DIFFERENT STAGES OF CHRONIC LYMPHOCYTIC LEUKEMIA ACCORDING TO RAI'S CLASSIFICATION.

Kotlarek-Haus S, Podolak-Dawidziak M, Frydecka I, Niewolna M, Smakowska E, Werynska B, Brodzka W
Klinika Hematologiczna, Instytut Chorob Wewnetrznych Akademii Medycznej, ul. Pasteura 4, 50-367 Wroclaw, Poland
Pol Arch Med Wewn; 65(3):211-218 1981

Correlations between clinical stage according to Rai's classification on one hand, and serum immune globulin and acid phosphatase activity of lymphocytes, on the other hand, were studied in 101 patients (63 men and 38 women, 32-76 yr old) with chronic lymphocytic leukemia. The mean survival was determined for 95 patients: with a group av of 5.2 yr, the mean survival was 12.7 yr in Stage 0, 5.7 yr in I, 5.5 yr in II, 3.6 yr in III, and 3.2 in IV. Thirty one patients died, 9/43 were in Stage I, 8/21 in Stage II, 7/11 in III, and 7/13 in IV. The total serum protein level was 6.6-6/9 g% in the different stages, vs 7.08 g% in 20 healthy controls. The percentage of 2.0% in III, and 12.9% in IV, vs 16.8% in the controls. The IgA levels were significantly lower in all stages of the disease than in the control, but relatively lowest in Stage III and highest in I and 0. The IgG levels were lowest in Stages III and IV. The IgM and acid phosphatase levels failed to reflect the progression of the disease. (13 Refs) (In POL)

10. THE DIAGNOSTIC SIGNIFICANCE OF T- AND B-ROSETTE FORMATION AND NON-SPECIFIC ACID ESTERASE IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE AND CHRONIC LEUKEMIA.

Gudat F, Albrecht R, Kasper M, Krey G, Durmuller U, Heitz Ph, Ludwig Ch, Christen Ch, Obrecht JP
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Schweiz Med Wochenschr; 111(36):1325-1330 1981

The diagnostic significance of acid non-specific alpha-naphthyl-acetate esterase (ANAE) and of rosette formation of

leukemic cells with sheep and mouse RBC was studied in 8 patients with acute myeloid leukemia (AML), in 4 patients with acute lymphatic leukemia (ALL) and in 14 patients with chronic lymphatic leukemia (CLL). ANAE showed typical diffuse cytoplasmic activity in all cases of AML. The enzyme activity was granular in both of the lymphoid malignancies, T-ALL and B-CLL, allowing differentiation from AML but not between B- and T-leukemia cells. Rosette formation with mouse RBC (ME) was diagnostic in all 14 cases of CLL and superior to labeling of surface Ig (8 of 14 cases positive). ME-rosette forming myeloblasts were detected in two of four evaluated cases of AML. Rosette formation with sheep RBC (SE), including cytological evaluation of rosette-forming cells, was diagnostic in all cases of ALL (= T-ALL). In six of nine patients with AML, however, rosette formation with SE was observed in a few cells, including myeloblasts with Auer rods. The occurrence of blasts in myeloid leukemia carrying lymphoid cell markers is discussed in the light of recent findings, according to which lymphoblastoid cells may arise in the course of myeloid leukemia requiring antileukemic treatment different from that of AML. (Author abstract) (18 Refs) (In GER)

11. HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE ACTIVITY IN NORMAL AND LEUKAEMIC LYMPHOCYTES.

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Br J Haematol; 49(1):23-28 1981

The levels of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) were determ ined in lymphocytes from normal people and patients with chronic lymphocytic leukemia (CLL). The HGPRT level in the total lymphocyte population from patients with CLL was lower than that from normal subjects. The HGPRT activity was higher in normal non-T cells than normal T cells. The enzyme activity in CLL B cells was lower than in CLL T cells. The HGPRT level was higher in CLL T cells than in normal T cells; these data suggest CLL T cells differ biochemically from their normal counterparts. (Author abstract) (17 Refs)

12. CAMP CONTENT IN T AND B LYMPHOCYTES IN PERIPHERAL BLOOD OF HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

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Pol Arch Med Wewn; 65(4):287-293 1981

The intracellular cyclic AMP (cAMP) levels were determined in isolated peripheral T and B lymphocytes from 12 healthy blood donors and 14 patients (8 men and 6 women, 33-75 yr old) with chronic lymphocytic leukemia. The intracellular cAMP levels (in picomole/10(7) cells) were 26.70 +-4.80 in the T cells and 43.30 +-6.30 in the B cells of the donors, and significantly decreased in the leukemia patients (12.50 in the T cells and 4.50 in the B cells). After excluding the five patients in clinical Stages 0 and I, the mean cAMP levels were even lower: 10.8 in the T cells and 4.90 in the B cells. The observed decrease in the intracellular cAMP concentrations in leukemic lymphocytes is attributed to immunological and functional immaturity of the B cells. (18 Refs) (In POL)

13. DNA SYNTHESIS IN THYMIC-ACUTE LYMPHOBLASTIC LEUKAEMIA.

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Br J Haematol; 48(4):585-594 1981

Deoxyribonucleoside triphosphate (dNTP) concentrations were measured in bone marrow and peripheral WBC from seven patients with acute Thy-lymphoblastic leukemia (Thy-ALL), 12 patients with acute myeloblastic leukemia and 15 patients with acute non-T, non-B lymphoblastic leukemia (c-ALL), and in thymocytes from patients with myasthenia gravis. Labeled thymidine and deoxycytidine incorporation into DNA was also studied. In Thy-ALL, dNTP concentrations were markedly increased compared with those in the other acute leukemias. The dNTP concentrations in thymocytes were, however, similar to those in Thy-ALL. 3H-nucleoside incorporation studies showed a marked difference in labeled deoxycytidine incorporation and particularly in the deoxycytidine/thymidine DNA labeling ratio between Thy-ALL and the other cell types. We conclude that the pathways of DNA synthesis in Thy-ALL blasts are different from those in the cells from other acute leukemias and some but not all these differences may correspond to differences between normal cortical thymocytes and bone marrow cells. (Author abstract) (37 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

14. SURFACE PHENOTYPE OF JAPANESE ADULT T-CELL LEUKEMIA CELLS CHARACTERIZED BY MONOCLONAL ANTIBODIES.

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Blood; 58(3):645-647 1981

We studied the surface phenotype and the functional activities of leukemic cells from three patients with Japanese adult T-cell leukemia (ATL) using the panel of OK and anti-Tac monoclonal antibodies, which react with differentiation antigens and define functionally distinct T-cell subsets or activated and terminally differentiated to T cells. The phenotype of ATL cells were determined to be OKT1+T3+T4+T10+T5-T8-OKIa1-, although cells from two patients suppressed pokeweed mitogen (PWM) induced normal B-cell differentiation, and cells from all patients lacked helper activity in this system. In addition, after cultivation with PWM, ATL cells from all patients were reactive with anti-Tac monoclonal antibody, and cells from one patient were reactive with OKIa1. These findings suggest that ATL cells arise from peripheral mature T-cell subsets and also suggest that the transition of surface phenotype of ATL cells to functionally mature and activated T cells occurs in culture. (Author abstract) (17 Refs)

15. CLASSIFICATION OF ACUTE LEUKEMIA BY SURFACE MARKERS AND CORRELATION WITH DIAGNOSTIC MORPHOLOGIES. RESULTS OF 111 CASES.

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Schweiz Med Wochenschr; 111(41):1524-1526 1981

One hundred eleven patients with acute leukemia, including 29 children, were classified according to the surface markers and cytochemistry of their blasts. The acute leukemias were separated into two major groups (lymphoid and non-lymphoid) depending on the presence or absence of specific lymphoid markers. On the basis of these criteria a correlation of 94% with the hematological diagnosis was obtained. Acute lymphoblastic leukemia (ALL) was divisible into three sub-groups: 11 cases expressing T-cell specific markers were classified as T-ALL and 33 cases expressing the common ALL antigen (CALLA) as c-ALL. Eighteen of the latter expressed an additional marker, DSA (Daudi surface antigen) splitting c-ALL cases in two subgroups. Cytochemistry of the cases lacking specific surface markers (n = 67) served to diagnose 41 acute myeloid leukemia (AML) cases and 8 monoblastic leukemias. The remaining 18 cases could n ot be classified. The presence or absence of HLD-DR (Ia) antigens served to subdivide AML into two major subgroups. The prognostic significance of these new diagnostic splits is under active study. (Author abstract) (3 Refs) (In FRE)

16. PROGNOSTIC SIGNIFICANCE OF THE T-CELL-MARKER IN CHILDHOOD ACUTE LYMPHATIC LEUKEMIA.

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Schweiz Med Wochenschr; 111(41):1527-1531 1981

Of 58 children with acute lymphatic leukemia who had undergone marker studies of blasts, only 6 (10%) had greater than 30 E+ blasts. Of these, five had a high WBC and organomegaly, but only two suffered a fatal course. Two more have been in CCR for over 5 yr despite other risk factors. Patients with less than 30% E+ cells did not differ from common ALL patients clinically or in their response to treatment. However, three older children with Hp-positive but E negative blasts had a very high WBC and died without having remission. Only standardized marker studies, treatment and follow-up of a large series of ALL patients will show the importance to be attached to these and other T-cell markers compared with the better-known clinical and hematologic risk factors. (Author abstract) (3 Refs) (In GER)

17. INVERSE CORRELATION OF ANTIVIRAL ANTIBODY TITERS AND THE REMISSION LENGTH IN PATIENTS TREATED WITH VIRAL ONCOLYSATE: A POSSIBLE NEW PROGNOSTIC SIGN IN ACUTE MYELOGENOUS LEUKEMIA.

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Cancer; 48(6):1363-1367 1981

In a study conducted since August 1974 by the Swiss Group for Clinical Cancer Research, 57 of 107 patients suffering from acute myelogenous leukemia achieved a complete remission. Thirty of these 57 patients were randomly selected to receive maintenance chemotherapy alone; the other 27 patients received, in addition to the same chemotherapy, monthly injections of viral oncolysate (ie, formalin-treated fowl plague virus-infected allogenous leukemia cells). The levels of antifowl plague virus antibody titers in the sera were determined at regular intervals. All patients with an initial antibody titer of zero and a titer increase after the very first injection of oncolysate had remission times of less than 6 mo (p less than or equal to 0.02). After the fifth injection there was a clear reverse correlation of titer values and remission lengths (p less than or equal to 0.01). Several patients showed an association of changes of antiviral antibodies in the serum and the percentage of myeloblasts in the bone marrow. Immunization by viral oncolysate can therefore be used to predict the course of patients who are in remission from acute myelogenous leukemia; it may furthermore be helpful in detecting patients whose treatment has been insufficient. (Author abstract) (16 Refs)

18. IMMUNOLOGIC EVALUATION IN THE PROGNOSIS OF ACUTE LYMPHOBLASTIC LEUKEMIA. A REPORT FROM CHILDRENS CANCER STUDY GROUP.

Leikin S, Miller D, Sather H, Albo V, Esber E, Johnson A, Rogentine N, Hammond D
Childrens Cancer Study Group Operations Office, 1721 Griffin Ave., Los Angeles, CA, 90031
Blood; 58(3):501-508 1981

Eight-hundred ninety-five previously untreated acute lymphoblastic leukemia (ALL) patients were entered on a protocol designed to provide results of selected immunologic tests. At diagnosis, delayed hypersensitivity tests with four antigens (tetanus, diphtheria, candida, and SKSD), Ig levels, tests for serum inhibition to phytohemagglutinin-stimulated lymphocyte blastogenesis, and HLA-A, B and C typing were performed. Although delayed hypersensitivity to antigens and serum inhibition of lymphocyte blastogenesis have been reported previously to be abnormal in ALL, we did not find them to be associated with disease outcome. Thirty percent of the patients had reduced levels of one or more Ig. The frequency of remission was less in those patients with decreased IgG and IgA. IgA and IgM showed prognostic importance in remission duration, and all three fractions appeared to have prognostic significance for survival duration. Although none of the HLA types appeared to be associated with significantly increased or decreased success in remission induction, patients with antigens A28 or B12 and patients bearing lymphocyte A11/B35 had shorter remissions. Our results indicate that of the immunologic factors studied, hypogammaglobulinemia and certain HLA antigens may be related to disease control and outcome in ALL. (Author abstract) (27 Refs)

19. CIRCULATING IMMUNOCOMPLEXES IN LEUKEMIA.

Mod A, Carpentier N, Fust Gy, Lambert PH, Miescher P, Hollan Zs
Orszagos Haematologial es Vertranszfuzios Intezet, Budapest, Hungary
Orv Hetil; 122(29):1757-1762 1981

The circulating immunocomplex (CIC) levels were determined in the blood serum of 113 patients with leukemia by three different methods (125 I-C1q-binding test, complement consumption test, and C1q solubility test). Acute myeloid leukemia was diagnosed in 54 cases, acute lymphocytic leukemia in 11, chronic myelocytic leukemia in 22, and acute lymphocytic leukemia in 26. Increased CIC level was demonstrated by at least two of the three tests in 64% of the patients. The repeated determinations revealed a relationship between the immuno-

complex level and the stage of the disease: the CIC level was higher during blast crisis than during remission. The CIC levels were often increased during infections as well. The CIC level also showed fluctuations regardless of the clinical picture, and the fluctuations demonstrated by the different test methods often failed to parallel with one another. The findings suggest that the circularing immunocomplexes occurring in leukemias are heterogeneous and their composition is subject to variations in the course of the disease. (25 Refs) (In HUN)

20. IMBALANCE OF T-CELL SUBPOPULATIONS DOES NOT RESULT IN DEFECTIVE HELPER FUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

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Cancer; 48(8):1754-1760 1981

The T-lymphocyte subpopulations identified by the Fc receptors for IgG (TG cells) and IgM (TM cells) in 12 patients with B-cell chronic lymphocytic leukemia (CLL) were quantitated and studied for functional capabilities in an in vitro assay. The TG cells in patients were elevated in relation to age- and sex-matched normal controls (p less than 0.05) resulting in an altered TM/TG ratio of 1.8 +-0.76 in CLL versus 5.9 +-3.7 in controls (mean +- SD, p less than 0.001). Despite this altered TM/TG ratio, the functional capability of the CLL T cells to regulate the terminal differentiation of B cells was found to be normal as reflected by the mean helper-suppressor score of 0.77 +-0.13 (+- SEM) obtained for both patients and controls. This unimpaired capacity of the T cells from CLL patients to help normal B cells mature into Ig-secreting cells indicated that hypogammaglobulinemia and monoclonal serum Ig in these patients may be a result of either an intrinsic defect in the B lymphocytes or their replacement by a neoplastic clone rather than a defect in the immunoregulatory T cells. (Author abstract) (39 Refs)

21. T-LYMPHOCYTES IN B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA.

Foa R, Catovsky D, Lauria F, Zafar MN, Galton DA
Istituto di Medicina Interna, Ia Cattedra di Patologia Speciale Medica, Corso Polonia, 14, 10126 Torino, Italy
Haematologica (Pavia); 66(1):105-116 1981

Functional properties of T-lymphocyte cells in B-cell chronic lymphocytic leukemia (B-CLL) were studied, including distribution of the major T-lymphocyte subsets: helper (Tmu) and suppressor (Tgamma) cells. Isolated T-lymphocytes in B-CLL failed to transform normally when cultured in the presence of the plant mitogen phytohemagglutinin (PHA) in 4/9 cases. T-colony-forming capacity was impaired in 12/16 cases. Significant imbalance in T-cell subset distribution was demonstrated in patients tested: the proportion of Tgamma cells is significantly higher in more advanced stages of B-CLL. Percentage of Tmu cells appears not related to disease stage; it was significantly reduced in most patients. The role of T-lymphocyte functional abnormalities in B-CLL is discussed, with review of findings reported in the literature. (53 Refs)

22. THE PRESENCE OF LYMPHOBLASTS IN THE GINGIVAL CREVICE OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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J Peridontol; 52(5):276-279 1981

Cells from the mouth were compared in 10 children with newly diagnosed acute lymphoblastic leukemia (ALL) and 10 normal controls. Expectorate produced by vigorous rinsing with 25 ml sterile saline was centrifuged and the resultant pellet studied. Smears of the cell suspension were stained with Wright's stain and PAS stain. Significantly fewer live oral cells were found in the ALL patients than in the controls. In controls, the predominant cell type was polymorphonuclear WBC (PMNL: av 84%); most of the remaining cells were lymphocytes (15.7%), with a few monocytes and eosinophils being observed. In the ALL group, the predominant cell type was lymphoblast (av 78.6%); remaining cells were chiefly lymphocytes (7.2%) and PMNL (13.8%). In both groups the differential oral cell counts reflected differential peripheral blood counts. Peripheral blood examination of the ALL patients revealed 12.2% PMNL, 0% lymphocytes, 1.2% monocytes, 1.7% eosinophils, 0.2% basophils, and 84.7% lymphoblasts. The findings suggest that leukemic lymphoblasts possess the same migratory abilities as normal lymphocytes. (15 Refs)

23. MOLECULAR WEIGHT ANALYSIS OF FCGAMMA-BINDING PROTEINS OF LYMPHOID LEUKEMIA, MYELOID LEUKEMIA, AND HAIRY-CELL LEUKEMIA.

Stein H, Thoenes J, Klatt U, Gerdes J, Muller V, Havsteen B
Inst. Pathology, Univ. Kiel, Hospitalstrasse 42, D-2300 Kiel, W. Germany
J Cancer Res Clin Oncol; 101(1):75-80 1981

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) previously indicated that a membrane protein isolated from the EDTA-mercaptoethanol lysates of B-cell lymphocytic leukemias had an apparent mol wt of 28,000 daltons. The protein bound to the Fc-region of IgG molecules. SDS-PAGE analysis of Fcgamma-binding proteins from two patients with chronic myeloid leukemia revealed a 42,000-and an 18,000-mol-wt protein. The Fcgamma-binding material from two hairy cell leukemias electrophoresed in the form of a closely spaced double peak in the 28,000-mol-wt region. Subsequent autoradiographic SDS slab gel electrophoresis revealed that one component of the double peak had a mol wt of 28,000 daltons and corresponded to the Fcgamma-binding material of the B-type lymphocytic leukemia cells. The second component had a lower mol wt and was not present on lymphoid or myeloid cells. These findings argue against a relationship between hairy cells and myeloid cells and in favor of a relationship between hairy cells and B cells. (16 Refs)

24. E-ROSETTE FORMATION IN B-CELL LYMPHATIC LEUKEMIAS INDUCED BY BINDING ACTIVITY OF MONOCLONAL SURFACE IMMUNOGLOBULINS TO SHEEP RED BLOOD CELLS.

Mitrou PS, Bergmann L, Holloway K, Zerth G
Dept. Internal Medicine, Div. Hematology/Oncology, Johann Wolfgang Goethe Univ., Frankfurt, W. Germany
Clin Immunol Immunopathol; 20(3):346-353 1981

The cells of a chronic lymphocytic leukemia (CLL) and a prolymphocytic leukemia (PLL) formed rosettes with sheep

RBC (SRBC) and expressed characteristic surface markers of B cells, ie, monoclonal surface IgM, Ia-like antigen, and receptors for aggregated IgG. Rosette formation was demonstrated to be the result of binding activity of surface Ig to SRBC. Pretreatment of the leukemic cells with Pronase, or antibodies to mu, lambda, or kappa, chains, respectively, completely inhibited rosette formation with SRBC. Preincubation of SRBC with serum of IgM fraction of the patient with PLL decreased rosette formation demonstrating circulating antibodies to antigen(s) on SRBC. The serum and IgM fraction of the patient with CLL agglutinated and lysed SRBC. The antigen(s) on SRBC involved in rosette formation were not related to Forssman or Paul Bunnel antigen. (Author abstract) (20 Refs)

25. CHEMOIMMUNOTHERAPY WITH LEVAMISOLE IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Pavlovsky S, Muriel FS, Garay G, Svarch E, Braier J, Lagarde M, Scaglione C, Eppinger-Helft M, Failace R, Dibar E
Instituto de Investigaciones Hematologicas, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina
Cancer; 48(7):1500-1507 1981

Patients with acute lymphoblastic leukemia (ALL) who were in two consecutive protocols and in complete remission (CR) with maintenance therapy, were randomized to receive or not receive levamisole. A total of 15 of 55 low-risk patients of protocol 10-LLA-72 with levamisole had relapses, compared with 25 of 54 not receiving levamisole; 67 and 49%, respectively, remain in CR at 48 mo (p less than 0.025). In protocol 1-LLA-76, 14 of 91 low-risk patients on levamisole and 25 of 93 patients not receiving levamisole had relapses; 78 and 61%, respectively, remain in CR at 36 mo (p less than 0.05). Seventeen of 39 high-risk patients (children with a WBC count higher than 50,000 and adults) receiving levamisole had relapses compared with 37 of 61 not on levamisole. The DNCB skin test shows at 18 and 24 mo a 74 and 85% positivity in the levamisole group vs a 38 and 35% positivity in the control group (p less than 0.025). We conclude that levamisole prolongs the duration of CR and survival in low-risk patients with ALL. (Author abstract) (35 Refs)

CHEMOTHERAPY

26. INTENSIVE CHEMOTHERAPY IS THE TREATMENT OF CHOICE FOR ELDERLY PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA.

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Blood; 58(3):467-470 1981

One-hundred and seven patients with acute myelogenous leukemia (AML) ranging in age from 15 to 82 yr who were previously untreated, received a 7-day high-dose remission induction regimen con sisting of danorubicin, cytarabine, and thioguanine (TAD). Identical complete remission rates of 76% were observed for 33 patients 60 yr of age and older and for 74 patients age 15-59 yr. Median remission duration and survival were 14 mo and 22 mo for patients 60 yr and older, and 16 mo and 22 mo for patients 15-59 yr. These differences are not significant. These data indicate that older patients respond to intensive chemotherapy in a similar manner to younger patients with this disease. (Author abstract) (20 Refs)

27. TREATMENT OF PATIENTS OVER 50 YEARS OF AGE WITH ACUTE MYELOGENOUS LEUKEMIA WITH A COMBINATION OF RUBIDAZONE AND CYTOSINE ARABINOSIDE, VINCRISTINE, AND PREDNISONE (ROAP).

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Blood; 58(3):584-591 1981

We administered a combination of rubidazone, cytosine arabinoside, vincristine, and prednisone (ROAP) to 91 patients with acute myelogenous leukemia who were 50 yr of age or older. These patients had been identified in previous studies to be a group with a relatively poor prognosis. One-third of the patients had an antecedent hematologic disorder prior to treatment. Forty patients (48%) obtained a complete hematologic and clinical remission. A history of an antecedent hematologic disorder, male sex, and absence of Auer rods were adverse factors for achieving remission in this older population. More than half of the patients achieved remission in one course. The major cause of failure to obtain a remission was death due to infection, 40% of which were caused by fungi. Resistance to chemotherapy, although uncommon, was noted more frequently in patients with an antecedent hematologic disorder. Univariate and multivariate prognostic factor analysis was used to compare these patients with a historical control group treated with a program in which adriamycin was used instead of rubidazone (AdOAP). No significant difference in remission rate was detected. Cyclocytidine was used as a maintenance agent in this study, and while the median remission duration was only 37 wk, 30% of patients are expected to be in remission for 2 yr. Chemotherapy programs combining an anthracycline with cytosine arabinoside, given to older patients in similar fashion to younger patients will achieve remissions in one-half of a group of older patients. These remissions are of comparable quality to those of younger patients. Mathematical models derived from analysis of prognostic factors are of use in identifying patients likely to fail these programs who are in need of innovative approaches to treatment. (Author abstract) (29 Refs)

28. LATE MARROW RECURRENCES IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA.

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Dept. Haematology, Hosp. for Sick Children, Great Ormond St., London WC1N 3JH, England
Br Med J; 283(6294):749-751 1981

Thirty children with acute lymphoblastic leukemia had a recurrence in the bone marrow after treatment was stopped electively. A second hematological remission was achieved in 27 (90%), and the median duration of remission was shortest (6 mo) in those relapsing within 6 mo of stopping treatment. Four of six children relapsing over 1 yr after stopping treatment remained in second hematological remission. Leukemic infiltration of the CNS developed in four patients remaining in marrow remission. It is concluded that conventional chemotherapy is unlikely to be effective in children with acute lymphoblastic leukemia who relapse soon after stopping treatment, that 'reprophylaxis' of the CNS probably with long-term intrathecal chemotherapy is essential, and that some patients relapsing after prolonged unmaintained remission may achieve long-term leukemia-free survival. (Author abstract) (10 Refs)

29. THE PHARMACOKINETICS OF SUBCUTANEOUS CYTOSINE ARABINOSIDE IN PATIENTS WITH ACUTE MYELOGENOUS LEUKAEMIA.

Slevin ML, Piall EM, Aherne GW, Johnston A, Sweatman MC, Lister TA

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Br J Clin Pharmacol; 12(4):507-510 1981

The pharmacokinetics of sc and iv bolus and iv infusion of cytosine arabinoside (araC) were compared in five adults with untreated acute myelogenous leukemia. All patients received araC (100 mg/square meter [m2] bid) for 7 days. Additional therapy consisted of adriamycin, 25 mg/m2 on days 1, 2 and 3, and 6-thioguanine, 200 mg/m2 for 7 days. Studies were performed on days 1-3 of therapy. On day 1 patients received araC by iv bolus injection, and on day 2 by sc bolus injection. On day 3 araC was given by continuous iv infusion, but it was initiated with a loading dose in order to achieve steady state rapidly. Pharmacokinetic parameters were determined from the semilog plot of plasma araC level vs time, using the interactive computer program STRIPACT. Study of mean plasma concentration vs time showed that after iv bolus injection, araC level declined tri-exponentially. After sc administration, a rapid absorption phase was followed by a bi-exponential decline. Plasma araC declined rapidly after iv bolus and sc bolus injection, and fell below steady state infusion level after av 40 min (iv bolus) and av 100 min (sc bolus). Terminal half-lives of the iv bolus, sc injection, and post-discontinuation of iv infusion were similar except for two erratic values following iv bolus in two patients. The study indicates that it is not possible to achieve comparable steady state levels of araC with the same total dose given by sc bolus as by continuous iv infusion. (10 Refs)

30. CLINICAL APPLICATION OF OMMAYA RESERVOIR FOR ADULT CNS LEUKEMIA.

Akao Y, Naito K, Yoshikawa H, Naoe T, Hiraiwa A, Yoshikawa S, Nakamura K, Uno H, Yamaguchi H

Dept. Internal Medicine, Nagoya First Red Cross Hosp., Nagoya, Japan

Rinsho Ketsueki; 22(5):624-629 1981

Ommaya reservoirs (sc cerebrospinal-fluid pouches) were used in treatments of a 40-yr-old woman with acute lymphogenous leukemia, a 44-yr-old man with acute lymphogenous leukemia, and an 18-yr-old woman with acute lymphogenous leukemia. The first woman had complete remission of systemic leukemia for 2 mo, but CNS-leukemia occurred. The CNS-leukemia was treated with intrathecal methotrexate (MTX), hydrocortisone, and cytosine arabinoside (CA) with intermittent success; the patient was also given 2,100 rads of 60Co radiotherapy to the cephalic region. Control of the leukemia was not possible with these methods, so an Ommaya reservoirs was used to deliver MTX. The male patient also was given MTX by means of an Ommaya reservoir to treat meningeal leukemia, but both patients died of systemic leukemia without evidence of meningeal leukemia. The second woman was treated with an Ommaya reservoir in order to drain cerebrospinal fluid to decrease intracranial hypertension. No side effects of the Ommaya reservoirs were noted in the three patients. The results indicated that the Ommaya reservoir is a valuable method for intrathecal delivery of chemotherapeutic agents in adults with meningeal leukemia. (13 Refs) (In JPN)

31. METHOTREXATE IN THE PLASMA AND CEREBROSPINAL FLUID OF CHILDREN TREATED WITH INTERMEDIATE DOSE METHOTREXATE.

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Acta Paediatr Scand; 70(5):615-618 1981

Serious complications can follow treatment with intermediate dose methotrexate of acute lymphoblastic leukemia in childhood. Toxicity has been shown to be correlated to plasma methotrexate concentrations. during iv infusions of methotrexate (500 mg/m(2)) the mean concentrations achieved 1 to 4 1/2 hr after the start of infusion were 1.3 x 10(-7) mol/l in cerebrospinal fluid and 1.7 x 10(-5) mol/l in plasma. At 72 hr after start of methotrexate infusion, plasma methotrexate concentrations were significantly higher in cases with symptoms of toxicity. In all the children who developed toxic symptoms 72-hr plasma methotrexate concentration was above 1 x 10(-7) mol/l. Assuming that leucovorin is given 48 hr after the start of methotrexate infusion, 74-hr plasma methotrexate is suitable for detection of patients at risk for toxicity. In children treated with intermediate dose methotrexate we therefore recommend estimating plasma methotrexate concentration 72 hr after the start of infusion, and instituting supplementary leucovorin when plasma methotrexate concentration exceeds 1 x 10(-7) mol/l. (Author abstract) (10 Refs)

RADIOTHERAPY

32. SPLENIC IRRADIATION IN B-PROLYMPHOCYTIC LEUKAEMIA.

Oscier DG, Catovsky D, Errington RD, Goolden AW, Roberts PD, Galton DA

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Br J Haematol; 48(4):577-584 1981

Twelve patients with B-cell prolymphocytic leukemia (PLL) were treated with splenic irradiation at a weekly dose of 100 cGy to a max total dose of 1,000 cGy. There was no morbidity associated with this treatment. Seven patients responded. Three achieved a good response and four a partial response. Two of the patients who had a partial response have subsequently died of unrelated causes. Four of the five patients who failed to respond have died as a result of their disease. When more than 25% of the prolymphocytes formed rosettes with mouse red blood cells (MRBC) the patients appeared to respond better to splenic irradiation. There was no correlation between response and the initial white cell count or the size of the spleen. (Author abstract) (9 Refs)

MULTIMODAL THERAPY

33. A COMPARISON OF MARROW TRANSPLANTATION WITH CHEMOTHERAPY FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN SECOND OR SUBSEQUENT REMISSION.

Johnson FL, Thomas ED, Clark BS, Chard RL, Hartmann JR, Storb R

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N Engl J Med; 305(15):846-851 1981

Twenty-four children with acute lymphoblastic leukemia (ALL) treated with cyclophosphamide, total-body irradiation, and marrow transplantation during a second or subsequent remission were followed for 17-55 mo; their progress was compared with that of 21 children treated with conventional chemotherapy during second or subsequent remission. During the follow-up period, 9/24 patients receiving marrow transplantation remained in complete remission, both in the blood and in the CNS, while 1/21 patients treated with conventional chemotherapy remained in remission after 20 mo. In the transplant group, 8/9 in continuing remission were well, not receiving maintenance therapy, and not requiring outpatient follow-up more often than every 1-3 mo. The one child receiving conventional chemotherapy who remained in remission required outpatient follow-up chemotherapy every 2 wk. Overall, in the transplantation group, 46% are alive, 38% have never relapsed, and 33% are well, compared with 10% alive, 5% in remission, and 5% well in the chemotherapy group. The major cause of failure in both groups was relapse. Acute and chronic graft-vs-host disease in the transplantation group and leukoencephalopathy in both groups were the major causes of morbidity and mortality. Thus, marrow transplantation offers the best chance of long-term remission and potential cure in the child with ALL in second or subsequent relapse. (19 Refs)

34. PHAGOCYTIC ACTIVITY OF NEUTROPHIL LEUKOCYTES AND MONOCYTES DURING THE REMISSION OF ACUTE LEUKEMIA AFTER CHEMOTHERAPY AND IMMUNOTHERAPY WITH BCG VACCINE AND LEVAMISOLE.

Dosimov ZhB, Skorobogatova OV, Rumiantsev AG, Eremeev VS

Dept. Pediatrics, N. I. Pirogov Second Medical Inst., Moscow, USSR

Pediatriia; (8):26-28 1981

Phagocytic activity (PA) of neutrophils and monocytes was studied in 42 children (aged 3 to 14 yr) with acute lymphoid leukemia. All patients were in complete remission of 6-36-mo duration; the patients received continuous maintenance chemotherapy and/or immunotherapy with BCG vaccine and levamisole. There was a marked inhibition of PA of neutrophils and monocytes in the patients undergoing chemotherapy. PA of monocytes in children undergoing immunotherapy with BCG vaccine was comparable to that in healthy controls. (20 Refs) (In RUS)

SUPPORTIVE CARE

35. PLATELET SUPPORT IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION.

Bacigalupo A, Avanzi G, Van Lint MT, Reali G, Solda A, Adami R, Strada P, Barbanti M, Podesta M, Marmont A

Divisione di Ematologia, Ospedale San Martino, Genova, Italy

Haematologica (Pavia); 66(1):80-90 1981

Two hundred thirty-one randomly assigned platelet transfusions were given to 18 (7 severe aplastic anemia and 11 leukemia) patients undergoing bone marrow transplantation. Relevance of previous transfusions, time of platelet support, and human leukocyte antigen (HLA)-matching to platelet increments is evaluated. No complications related to the 231 apheresis were observed. The number of platelet transfusions ranged from 4-29/patient; a slight tendency for inverse correlation between number of transfusions and platelet increment was observed. No difference was seen in platelet increments between patients receiving long or short term support. Interval between transfusions did significantly influence platelet increment: 100% of patients transfused at intervals of 3 days or more exhibited mean increments greater than 5,000 defined units, whereas only 20% of patients transfused at intervals of less than 3 days had the same mean increments. Retrospective analysis of 128 HLA-typed transfusions indicated no correlation between HLA score and platelet increments. Refractoriness developed in 9/18 patients: 1 had received less than 10 transfusions and 8 had received greater than 10. In three patients refractoriness against HLA-identical platelets from the bone marrow allogeneic or syngeneic donor was also observed. Results indicated that HLA-matched platelets are of little benefit in patients receiving multiple random transfusions. Interval of time between transfusions appeared more relevant to overall platelet response than the total number of transfusions . (14 Refs)

36. IN VITRO REGULATION OF IMMUNOGLOBULIN SYNTHESIS AFTER MARROW TRANSPLANTATION. I. T-CELL AND B-CELL DEFICIENCIES IN PATIENTS WITH AND WITHOUT CHRONIC GRAFT-VERSUS-HOST DISEASE.

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Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104

Blood; 58(3):431-439 1981

Twenty-four patients with aplastic anemia or acute leukemia were treated by marrow grafts from HLA-identical donors after conditioning with high doses of cyclophosphamide and/or total body irradiation. They were studied between 4 and 63 mo (median 14.2) after transplantation. Seventeen patients had chronic graft-versus-host disease (C-GVHD) and 7 were healthy. They were studied for defects in their T- and B-cell function using an indirect hemolytic plaque assay for Ig production after 6 days of culture in the presence of pokeweed mitogen. T or B cells from the patients with or without C-GVHD were cocultured with T or B cells from their HLA-identical marrow donors or unrelated normal controls. Intrinsic B-cell defects, lack of helper T-cell activity, and suppressor T-cell activity were more frequently found in patients with C-GVHD than in healthy patients. Fifteen of the 17 patients with C-GVHD showed one or more defects in their T- and B-cell function compared to only 3 of the 7 patients without C-GVHD. None of the healthy controls, including the marrow donors, showed defects in their T- and B-cell functions. These

in vitro findings may be helpful in assessing the process of immune reconstitution and the immunologic aberrations found after human marrow transplantation. (Author abstract) (29 Refs)

37. SURVEILLANCE CULTURES.

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J Infect Dis; 144(1):81-84 1981

The usefulness of surveillance cultures for epidemiologic, preventive, and therapeutic research is discussed, and the situations in which surveillance cultures may be valuable in the management of patients with compromised host defense mechanisms are indicated. Serious illness, in the absence of antibiotic therapy, leads to alterations in the microbial flora at many body sites. Among 135 previously reported, consecutive, newly diagnosed patients with acute nonlymphocytic leukemia (ANLL), surveillance cultures of the nose, gingiva, and axillae revealed a substantial frequency of gram-negative bacilli, of which Escherichia coli was the most common. Sources from which a hospitalized patient may acquire new organisms included the hands of personnel (eg, Staphylococcus aureus), food (Candida albicans or Torulopsis glabrata), water (Pseudomonas aeruginosa), and dust particles (Aspergillus sp). During a 2-yr period, the author found that acquired flora caused about half of the infections that developed among a group of 48 patients with ANLL. New organisms were acquired at a rate of 1.24/patient/wk during the same period. The institution of a series of basic infection-prevention techniques reduced this rate to 0.51/patient/wk. P aeruginosa was found to be a particularly virulent organism, especially in patients with a granulocyte count less than 100/ul and in whom the alimentary-canal mucosa had been damaged by cytotoxic therapy. Although surveillance cultures are not needed in most situations, they are of value in monitoring patients isolated in rooms with laminar air flow and who are receiving po nonabsorbable antibiotics; in situations in which po nonabsorbable antibiotics are being used outside of reverse isolation; and in patients receiving selective microbial suppression. (10 Refs)

38. IMMUNITY TO VARICELLA-ZOSTER VIRUS IN CHILDREN WITH ACUTE LEUKEMIA OR OTHER MALIGNANCIES. PART 1. LYMPHOCYTE BLASTOGENIC RESPONSE TO VARICELLA-ZOSTER VIRUS ANTIGEN IN CHILDREN WITH ACUTE LEUKEMIA.

Ihara T

Dept. Pediatrics, Mie Univ., Tsu, Mie 514, Japan

Shonika Kiyo; 27(1):40-41 1981

Lymphocyte blastogenic response to Varicella-Zoster virus antigen was studied in 78 adults or children, including 11 children with acute lymphocytic leukemia (ALL) who had had varicella and 13 vaccinated children with ALL. Stimulation index values of healthy children and adults who had had varicella and of leukemic children who had had varicella or had been vaccinated were statistically higher than those children who had not been previously infected. Results indicated that lymphocytes of leukemic children in remission can respond normally to Varicella-Zoster virus antigens. (no Refs)

39. IMMUNITY TO VARICELLA-ZOSTER VIRUS IN CHILDREN WITH ACUTE LEUKEMIA OR OTHER MALIGNANCIES. PART 2. FOLLOW-UP STUDY ON IMMUNITY TO SPECIFIC VARICELLA-ZOSTER VIRUS AFTER VACCINATION OF LIVE VARICELLA VACCINE IN CHILDREN WITH ACUTE LEUKEMIA OR OTHER MALIGNANCIES.

Ihara T

Dept. Pediatrics, Mie Univ., Tsu, Mie 514, Japan

Shonika Kiyo; 27(1):42-43 1981

Various doses of live varicella virus vaccine were given to 16 healthy children, 37 children with acute lymphocytic leukemia, 1 with acute myelocytic leukemia, 4 with retinoblastoma, 3 with neuroblastoma, and 1 with malignant lymphoma to determine the optimal dose and the clinical response to the vaccination. The leukemic children responded well to doses of 100-1,500 PFUs. Live varicella vaccine was observed to be safe and effective about 6 mo after the complete remission of leukemia in leukemic children who were in hematological remission and in good immunological status. (no Refs)

40. PATTERNS OF OROPHARYNGEAL AND FECAL FLORA IN PATIENTS WITH ACUTE LEUKEMIA.

Fainstein V, Rodriguez V, Turek M, Hermann G, Rosenbaum B, Bodey GP

Dept. Developmental Therapeutics, Section Infectious Disease, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030

J Infect Dis; 144(1):10-18 1981

The oropharyngeal and fecal flora in 33 patients hospitalized with acute leukemia was examined. Normal flora predominated on admission. All patients received chemotherapy during the 48 hr after admission and at least one course of antibiotics during hospitalization. By the end of the study, 68% of the initial normal throat flora and 57% of the fecal flora had disappeared. The shift in flora was mainly due to the persistence or acquisition of aerobic gram-negative bacilli. Before antibiotics were given, the normal flora in both sites had already decreased in quantity, and increased numbers of aerobic gram-negative bacilli were found. After the first course of antibiotics, a further decrease in the total number of normal strains was observed. Information obtained from surveillance cultures was helpful for understanding the changes in flora but did not correlate with the microbiology of the infectious processes and could not be used to predict infection. (Author abstract) (19 Refs)

41. USE OF BIOLOGICAL PREPARATIONS FOR ABACTERIAL CORRECTION IN PATIENTS WITH ACUTE LEUKEMIAS.

Tolkacheva TV, Abakumov EM, Martynova VA, Golosova TV

Central Inst. Hematology and Blood Transfusion, Moscow, USSR

Probl Gematol Pereliv Krovi; 26(7):29-33 1981

The efficacy of various biological preparations for the abacterial correction (ABC) and prophylaxis of infectious complications was studied in 59 patients with acute leukemia. Group I (27) received polyvalent phages, Group II (9) received dry bacterial preparations containing bifidobacteria, Group III (10) received polyvalent phage followed by recolonization with bifidoflora, and Group IV (13) received nonabsorbable antibiotics (control). Antibiotics inhibited normal intestinal microflora and enhanced the ABC. The most effective correction of intestinal ABC was observed in Group III. (16 Refs) (In RUS)

42. PROPHYLACTIC TRIMETHOPRIM-SULFAMETHOXAZOLE DURING CONSOLIDATION CHEMOTHERAPY FOR ACUTE LEUKEMIA: A CONTROLLED TRIAL.

Weiser B, Lange M, Fialk MA, Singer C, Szatrowski TH, Armstrong D

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Ann Intern Med; 95(4):436-438 1981

We conducted a prospective, controlled, randomized trial of oral trimethoprim-sulfamethoxazole treatment in patients with acute leukemia receiving consolidation chemotherapy. We followed 14 treatment patients during 33 episodes and 15 control patients during 34 episodes of granulocytopenia (less than 1,000 granulocytes/mm3). We found no significant difference in the incidence of febrile episodes (13 in treatment group vs 24 in control group), hospitalizations to treat fever or infection (10 vs 12), number of documented infections (8 vs 10), number of septicemias (1 vs 2), or mean duration of hospital stay to treat fever or infection (8.9 vs 9.2 days) in the two groups. There was little colonization with organisms resistant to trimethoprim-sulfamethoxazole, including Candida, in either group. Prophylactic trimethoprim-sulfamethoxazole did not significantly reduce the incidence of fever, hospitalization, or infection in granulocytopenic patients during consolidation chemotherapy. (Author abstract) (11 Refs)

43. PROPHYLAXIS OF BACTERIAL INFECTION BY SULFAMETHOXAZOLE-TRIMETHOPRIM (SMX-TMP) DURING CHEMOTHERAPY IN PATIENTS WITH CHILDHOOD ACUTE LEUKEMIA.

Tono-oka T, Nakayama M, Ohkawa M, Nakajima T, Takeda T, Matsumoto S

Dept. Pediatrics, Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan

Tohoku J Exp Med; 134(3):273-279 1981

During induction chemotherapy, a combination of sulfamethoxazole and trimethoprim (SMX-TMP) was given po to 13 children (0.5-13 yr old) with acute leukemia on 16 occasions of hospitalization for prophylaxis of bacterial infection. Fourteen children with acute leukemia treated at an earlier period were used as a control group. The SMX-TMP group received 40 mg SMX and 8 mg TMP per kg per day, po, during induction chemotherapy. There were no definite differences in the methods of chemotherapy and supportive therapy between the two groups of patients. Slightly more episodes of neutropenia were noted in the SMX-TMP group than in the controls. Fever was experienced for 14.6% of the total hospital days by the control group compared to 6.6 days in the SMX-TMP group. In the control group approx 50% of the febrile episodes were due to definite infections, while most of the episodes in the SMX-TMP group were due to fever of unknown origin. In the control group, the frequency of one infection per one hospitalization was 1.0, and in the SMX-TMP group it was 0.25. In the control group, many of the infections were major, namely sepsis and pneumonia. In the SMX-TMP group, all the episodes of infection were minor such as urinary tract infection and otitis media. Thus, the administration of SMX-TMP to leukemic children during chemotherapy is recommended. (12 Refs)

44. FEVER IN NEUTROPENIC PATIENTS: ANALYSIS OF 109 EPISODES AND 15 SUPERINFECTIONS.

Baro J, Richard C, Esteban J, Iriondo A, Conde E, Garijo J, Zubizarreta A

Servicio de Hematologia, Centro Medico Nacional 'Marques de Valdecilla', Santander, Spain

Sangre (Barc); 26(4):417-426 1981

An analysis is offered of 109 febrile episodes appearing in 66 patients diagnosed as having acute non-lymphocytic leukemia, hypoplastic pancytopenia or agranulocytosis. The infectious nature of the episode could not be ascertained in 33 occasions (30%), was clinically confirmed in 14 (13%), and in 62 episodes (57%) was microbiologically documented. The clinically and/or microbiologically confirmed infections yield a mortality greater to that of the unconfirmed episodes (p less than 0.01). Among the confirmed infections and superinfection, the rate of bacteremia was 37/91 episodes (41%), no original focus being ascertained in 15 of them. Pulmonary infections were the commonest, followed by urinary tract ones. Digestive infectious localizations appeared commonly among the superinfectious episodes. The most frequently found agents were E coli, P aeruginosa, and klebsiella-enterobacter, followed by Candida. The global mortality rate was 29%, and it was conditioned by age (p less than 0.05), evolution of granulocytopenia (p less than 0.001), and infectious localization. Pneumonia, septicemia by Gram-negative germs and/or fungi, and digestive tract infections and superinfections showed higher mortality than the remaining infectious forms (p less than 0.001). (Author abstract) (26 Refs) (In SPA)

45. FUNGEMIA IN THE IMMUNOCOMPROMISED HOST. CHANGING PATTERNS, ANTIGENEMIA, HIGH MORTALITY.

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Am J Med; 71(3):363-370 1981

Fungemias were reviewed in 110 immunocompromised patients hospitalized between November 1, 1974, and December 31, 1977, at Memorial Sloan-Kettering Cancer Center (MSKCC). The incidence of Candida tropicalis fungemia increased each yr. Seventy-six percent of the patients with C tropicalis fungemia and 32.5% of those with C albicans fungemia had either leukemia or lymphoma. Seventy-seven percent of the C parapsilosis fungemias were related to total parenteral nutrition. Thirty-seven percent of the patients with C albicans fungemia were receiving oral prophylactic nystatin therapy. The source of fungemia was often difficult to determine: in 60% of the patients, only blood cultures were positive for C tropicalis or Torulopsis glabrata; no cultures were positive for the fungus from any other site before the episode occurred. Serologic tests, including a highly sensitive passive hemagglutination test, showed fourfold increases in titer only inconsistently. A passive hemagglutination-inhibition test for circulating antigen was positive in 50.9% of 57 patients with fungemia who were tested and may be a valid indication for treatment. Fungemia usually represented a severe and often fatal disease. The over-all mortality of the 110 patients with fungemia was 79% whereas only 23% of the patients with C parapsilosis fungemia died. Among the patients who received more than 200 mg of amphotericin B, 71% died despite treatment. (Author abstract) (22 Refs)

46. DETECTION OF ANTIBODIES AND ANTIGENEMIA IN LEUKEMIC PATIENTS WITH CANDIDIASIS BY ENZYME-LINKED IMMUNOSORBENT ASSAY.

Meckstroth KL, Reiss E, Keller JW, Kaufman L
(c/o Reiss) Mycology Div., Centers for Disease Control, Atlanta, GA, 30333
J Infect Dis; 144(1):24-32 1981

Standard tests and two enzyme-linked immunosorbent assays (ELISAs) were compared for detecting systemic candidiasis in 92 leukemic patients. Antibodies to Candida were detected by immunodiffusion (ID), latex agglutination (LA), and indirect ELISA; antigenemia was evaluated by indirect ELISA inhibition. In 48 patients without candidiasis (Group 1), sera from 27% reacted in ID and 13% in LA tests; titers of antibody by ELISA occurred in all patients. In 34 patients without disseminated candidiasis (Groups 2 and 3), Candida species were isolated; sera from 35% and 32% were positive in the ID and the LA test, respectively. In 9 of 10 patients with disseminated candidiasis (Group 4), LA and ID tests were negative. Seven patients in Groups 1-3 without disseminated candidiasis were antigenemic (false-positive rate, 9%). Antigenemia was detected in 7 of 10 patients with disseminated candidiasis; in the remaining three patients sera were drawn too early to be of diagnostic value. Thus, monitoring of immunosuppressed patients for mannan antigenemia is useful for the detection of disseminated candidiasis. (Author abstract) (12 Refs)

47. DENTAL CARE IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA.

Bertolone SJ, Burzynski NJ, Borden D
Dept. Pediatrics, Children's Hosp., 200 East Chestnut St., Louisville, KY, 40202
South Med J; 74(8):976-978 1981

To evaluate the dental status of children with acute lymphocytic leukemia in their first remission, we divided 41 children into age groups in accordance with the National Dental Health Survey. We used the DMF (decayed, missing, filled) index to evaluate dental disease and status of oral hygiene. The study groups had higher DMFs (2.2 vs 1.4), more decayed teeth (4.2 vs 1.7), and fewer filled (1.5 vs 3.8) teeth than the national av. There is no direct evidence that antileukemic therapy causes dental decay per se, but the level of oral hygiene may be substandard in children with acute lymphocytic leukemia. (Author abstract) (17 Refs)

48. PATTERNS OF COMMUNICATION AMONG PEDIATRIC PATIENTS WITH LEUKEMIA, PARENTS, AND PHYSICIANS: PROGNOSTIC DISAGREEMENTS AND MISUNDERSTANDINGS.

Mulhern RK, Crisco JJ, Carritta BM
Dept. Pediatrics, Medical Coll. Wisconsin, Milwaukee, WI, 53233
J Pediatr; 99(3):480-483 1981

The prognostic views of 25 pediatric patients with leukemia, their parents, and their physicians were assessed. Mothers, fathers, and physicians also estimated the prognostic views of each other as well as those of the children. Complex and subtle patterns of disagreement and misunderstanding were revealed. Physicians were generally less optimistic than mothers or fathers. Furthermore, mothers and fathers tended to overestimate physicians' views, whereas physicians tended to underestimate the prognostic views of mothers and fathers. Although children were more optimistic than their mothers, fathers, or physicians, parents understood this difference but physicians did not. These results suggest that disagreements and misunderstandings may be responsible for seemingly unusual or maladaptive patient and family coping. (Author abstract) (6 Refs)

CASE REPORTS

49. MALIGNANT LYMPHOMA SUPERVENING IN CHRONIC LYMPHOCYTIC LEUKEMIA AND RELATED DISORDERS. RICHTER'S SYNDROME: A STUDY OF 25 CASES.

Harousseau JL, Flandrin G, Tricot G, Brouet JC, Seligmann M, Bernard J
(c/o Flandrin) Laboratoire de Cytologie, Institut de Recherche sur les Leucemies et les Maladies du Sang, Hopital Saint-Louis, 75475-Paris Cedex 10, France
Cancer; 48(6):1302-1308 1981

Richter's syndrome (RS) has been defined as 'histiocytic' lymphoma (HL) or Hodgkin's disease (HD) supervening in the course of chronic lymphocytic leukemia (CLL) and related disorders. The clinical, histologic, and immunologic findings in 25 cases (11 women, 14 men) of RS are presented. The initial diagnosis was CLL in 19 cases, diffuse well-differentiated lymphocytic lymphoma in 2 cases, and Waldenstrom's macroglobulinemia in 4 cases. The interval between the initial diagnosis and that of RS ranged from 0 (2 cases) to 120 mo (median 49 mo). At the time of diagnosis of RS, the initial lymphoproliferative disorder was an apparent complete remission in only two cases. The lymphoma was disseminated in at least 18 cases. The overall median survival was 4 mo, but complete remission was achieved in six cases and has been maintained for 15 to 77 mo. In four of these six cases, the RS was localized. The histologic diagnosis of HD was made in only two cases. In the other 23 cases the diagnosis was HL, but in 5 of these cases, the proliferation was heterogeneous and was considered as an early aspect of HL. Immunologic studies of lymph node cell suspensions were performed in seven cases. In all cases, the B-lymphocytic origin of the lymphoma cells could be ascertained. Detailed studies in four cases showed that lymphoma cells carried SIg of the same isotype and light chain type as that of SIg detected on CLL cells or of monoclonal serum Ig. In these cases, the lymphoma was actually related to the initial B-cell chronic lymphoid disease. (Author abstract) (33 Refs)

50. SURVIVAL AFTER NECROTIZING ENTEROCOLITIS OF LEUKEMIA TREATED WITH ORAL VANCOMYCIN.

Freeman HJ, Rabeneck L, Owen D
Div. Gastroenterology, Dept. Medicine, Univ. British Columbia Health Sciences Center Hosp., 2211 Wesbrook Mall, Vancouver, British Columbia V6Y 1W5, Canada
Gastroenterology; 81(4):791-794 1981

A 56-yr-old female with chronic lymphocytic leukemia developed hemolytic anemia and thrombocytopenia. Prednisone therapy was instituted, but her disease was further complicated by the development of necrotizing enterocolitis. No specific enteropathogens were identified, and the stools were consistently negative for Clostridium difficile toxin. Treatment with vancomycin was instituted and resulted in complete recovery. In view of the high mortality and poor results of treatment in necrotizing enterocolitis, it is postulated that a further trial of this drug is justified. (Author abstract) (18 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

51. CHROMOSOME ABNORMALITIES IN DOWN'S SYNDROME PATIENTS WITH ACUTE LEUKEMIA.

Kaneko Y, Rowley JD, Variakojis D, Chilcote RR, Moohr JW, Patel D

Dept. Medicine, Box 420, Univ. Chicago, 950 East 59th St., Chicago, IL, 60637

Blood; 58(3):459-466 1981

Chromosome and cytologic studies were performed on three Down's syndrome (DS) patients with acute nonlymphocytic leukemia (ANLL). All three patients had an aneuploid clone in their leukemic cells: 50,XX, +6,19, +21, +22, 48,XX, +8, +21, and 47,XY, +8,-21, +dic(21:21)(p13;p11). Every patient appeared to have acute undifferentiated leukemia when the blast cells were examined with Wright-Giemsa stain; cytochemistry studies, however, showed that the leukemic blasts were in an early stage of myeloid differentiation. The two patients with +8 had a preleukemic phase; the blast cells of the patient with an extra number 19 and number 22 could not be differentiated morphologically from those of the two patients with an extra number 8. Our finding and a review of data on 40 other patients suggest that most DS children with ANLL have hyperdiploidy, which is usually related to gains of C, F, and/or G chromosomes, and that the abnormalities of +8 and of +19, +22 in DS children may be associated with acute leukemia (AL) in an early stage of myeloid differentiation. (Author abstract) (41 Refs)

SELECTED PRE-CLINICAL STUDIES

52. ULTRASTRUCTURAL, CELL MEMBRANE, AND CYTOGENETIC CHARACTERISTICS OF B-CELL LEUKEMIA, A MURINE MODEL OF CHRONIC LYMPHOCYTIC LEUKEMIA.

Slavin S, Weiss L, Morecki S, Bassat HB, Leizerowitz R, Gamliel H, Korkesh A, Voss R, Polliack A

Dept. Medicine, Immunology Res. Lab., Jerusalem, Israel

Cancer Res; 41(10):4162-4166 1981

A murine model of a spontaneous, transplantable BALB/c B-cell leukemia (BCL1) is described. Extreme leukemia and splenomegaly develop in H-2d-compatible recipients of tumor cells. Tumor cells are medium to large lymphocytes that can be transformed in plasmacytoid cells following in vitro stimulation with lipopolysaccharide. Karyotype analysis of transformed tumor cells reveals 36 chromosomes with several monosomies and 7 marker chromosomes. The ultrastructure of the tumor cells was studied using transmission and scanning electron microscopy. Although the appearance of tumor cells seems normal by morphological criteria, an impaired capping ability was documented using the fluorescein-conjugated concanavalin A-binding test. Impaired capping ability was documented before leukemia was overt as early as 1 to 3 days following inoculation of tumor cells. The B-cell leukemia (BCL1) provides a useful murine model for the study of various aspects of human bone marrow-derived malignant disorders. (Author abstract) (28 Refs)

53. ERADICATION OF DISSEMINATED MURINE LEUKEMIA BY CHEMOIMMUNOTHERAPY WITH CYCLOPHOSPHAMIDE AND ADOPTIVELY TRANSFERRED IMMUNE SYNGENEIC LYT-1+2-LYMPHOCYTES.

Greenberg PD, Cheever MA, Fefer A

Div. Oncology, Dept. Medicine, Univ. Washington Sch. Medicine, Seattle, WA, 98195

J Exp Med; 154(3):952-963 1981

The efficacy of T cell subpopulations, as distinguished by expression of Lyt antigens, was analyzed in adoptive chemoimmunotherapy (ACIT) of established murine leukemia and in in vitro assays for the generation and expression of cytotoxicity. The results demonstrated that the predominant donor effector cell required for eradication of advanced disseminated leukemia by ACIT is an immune Lyt-1+2-T cell that is not cytolytic in vitro. Immune cells depleted of Lyt-2+ cells, such that the only donor T cells remaining were of the Lyt-1+2-phenotype, were nearly as effective in ACIT as unselected cells suggesting that other donor T cell subsets do not provide an essential contribution. The potential therapeutic efficacy of immune cells was ablated nearly as completely by depletion of Lyt-1+ cells as by depletion of all T cells. The small residual anti-tumor effect still evident after treatment of immune cells with alpha-Thy-1.2 and complement probably reflected incomplete T cell removal. The T cell subset analyzed in ACIT were defined operationally by susceptibility to lysis by monoclonal antibody to Lyt antigens and complement. The results demonstrated that the phenotype of the predominant T cell subset required for efficacy in ACIT is Lyt-1+2-, which is distinct from the T cell phenotypes mediating in vitro tumor lysis. The mechanisms by which Lyt-1+2-cells can promote tumor rejection are discussed. (31 Refs)

54. ADOPTIVE IMMUNOTHERAPY AND COMBINED CHEMO-IMMUNOTHERAPY IN TRANSPLANTABLE LEUKAEMIA OF AKR MICE (TAL); OCCURRENCE OF NATURAL KILLERS.

Schneiberg K, Rytwinski K, Tabenska J

Instytut Onkologii, Oddzial w Gliwicach, ul. Armii Czerwonej 15, 44-010 Gliwice, Poland

Haematologia (Budap); 14(2):137-146 1981

Inbred AKR mice received transplantable AKR leukemia (TAL: 10(4)-10(5) viable lymph node cells from ill syngeneic donors) by ip injection. Effector cells were obtained from C57BL/6, DBA/2J, BALB/c, or syngeneic AKR donors. Some allogeneic donors had been preimmunized with AKR cells. Some recipients received donor cells irradiated before injection. Some received whole-body x-ray irradiation (300 rad) before injection of tumor cells. Intact mice injected with TAL, but not otherwise treated, survived longer than irradiated mice. Injection of allogeneic effector cells from non-immunized mice increased the survival time of intact TAL-bearing mice. Syngeneic effector cells had no effect. Thymocytes from non-immunized donors or lymph node cells from immunized donors increased survival time in irradiated mice. Injection of 50 mg/kg cyclophosphamide (CY) produced a 70% permanent survival rate. Injection of effector cells did not increase the effect of CY. Thymocytes from immunized or non-immunized donors increased survival time of mice not given CY. Mean survival increased as effector cell:target cell ratio increased from 10:1 to 1,000:1. Above 1,000:1 no increase was noted. Results indicate the existence of natural non-immune cytotoxic cells, directed against Gross virus-infected cells, in C57BL/6, DBA/2J, and

BALB/c mice, but not in AKR mice. These effector cells were present in many lymphoid organs. (31 Refs)

55. LEVODOPA AND DOPAMINE ANALOGS: DIHYDROXY AND TRIHYDROXYBENZYLAMINES AS NOVEL QUINOL ANTITUMOR AGENTS IN EXPERIMENTAL LEUKEMIA IN VIVO.

Wick MM
Charles A. Dana Cancer Center, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer Treat Rep; 65(9):861-867 1981

Levodopa and dopamine demonstrate significant antitumor activity in several experimental systems. We have prepared the nonneurotoxic dihydroxybenzylamine (DHBA) analogs 2,3-DHBA, 3,4-DHBA, and 2,5-DHBA and the trihydroxy derivatives 2,3,4-and 3,4,5-trihydroxybenzylamine. These analogs demonstrated significant and reproducible antitumor activity in the ip P388 and L1210 lymphocytic leukemias. This activity was markedly increased when the drugs were given by multiple injections tid for 4 days. 3,4-DHBA and 2,3-DHBA resulted in 30% and 20% long-term survivors, respectively. There was a selective inhibition of thymidine incorporations and a relatively lesser effect on uridine and leucine incorporation. Inhibitory concentrations were between 0.1 and 1.0 mM. The trihydroxy derivatives were more potent, with inhibitory concentrations between 0.01 and 1.0 mM. Furthermore, the trihydroxy derivatives were also able to inhibit the incorporation of uridine and leucine as well as thymidine. The para derivative, 2,5-DHBA, although a potent inhibitor in vitro, was completely inactive in vivo. When L1210 and P388 tumor-bearing animals were given radioactively labeled thymidine in vivo following the administration of drugs, a selective inhibition of thymidine incorporation by tumor cells was observed, with essentially no effect on gut or bone marrow. Doses greater than 200 mg/kg completely suppressed the incorporation of radioactively labeled thymidine by tumor cells 1 hr after administration of drug. A similar dose response was observed in the more slowly growing P388 leukemia, suggesting that the antitumor effect did not strongly correlate with growth rate of the tumor. Since levodopa and dopamine are currently being evaluated in patients with metastatic melanoma, the availability of analogs with enhanced antitumor activity and broader antitumor spectrum are of interest. (Author abstract) (18 Refs)

56. IN VIVO INHIBITION OF THE DEVELOPMENT OF MYELOID LEUKEMIA BY INJECTION OF MACROPHAGE- AND GRANULOCYTE-INDUCING PROTEIN.

Lotem J, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovoth 76100, Israel
Int J Cancer; 28(3):375-386 1981

Injection of macrophage- and granulocyte-inducing protein (MGI) can inhibit the development of myeloid leukemia in vivo and stimulate normal myelopoiesis. The MGI injected contained MGI-I activity that induces colony formation with normal myeloblasts, and MGI-2 activity that induces differentiation of normal and MGI 7+ 1D 7+ 1 leukemic myeloblasts to mature macrophages or granulocytes. Injection of MGI reduced the tumor vol in mice sc inoculated with leukemic cells at least 50-fold The median survival time of MGI 7+ 1D 7+ 1 cells or sc with MGI 7+ 1D 7-1 cells was increased by about 40%, and 50% of the MGI-treated mice inoculated sc with MGI 7+ 1D 7+ 1 cells did not develop tumors. MGI also increased the anti-tumor effect of cyclophosphamide. The leukemia-inhibiting activity in the injected MGI preparations was associated with the peak of MGI activity separated on a hydroxylapatite column and was destroyed by treatment at the temperature which destroys MGI-2 activity. This indicates that the inhibition of leukemia development was mediated by MGI-2. It is suggested that improved schedules of MGI treatment, with or without compounds used in the cytotoxic types of therapy, should be able to give an even better inhibition of leukemia development and that these results should also be applicable to the therapy of human myeloid leukemia. (61 Refs)

REVIEWS

57. PROGRESS IN THE TREATMENT OF CHILDHOOD ACUTE LEUKEMIA: A REVIEW.

Steinhorn SC, Myers MH
Biometric Res. and Analytic Studies Section, Biometry Branch/NCI, Landow Building, Room 5C19, Bethesda, MD, 20205
Med Pediatr Oncol; 9(4):333-346 1981

The dramatic improvements in the survival experience for children diagnosed with acute leukemia are analyzed using data collected through hospitals participating in the National Cancer Institute's End Results Group Program between 1950 and 1973. Children under 15 yr of age who were diagnosed with both acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL) showed moderate improvements in the 1950s, but beginning in the 1960s those with ALL did far better. Statistically significant differences at the 0.05 level were noted between their three-yr survival rates for all cohorts analyzed betwee n 1960 and 1973. For the 1970-1973 cohort, three-yr survival rates were 49% and 20% for ALL and ANLL, respectively, and five-yr survival rates were 34% and 12%. Between 1950 and 1976 the age-adjusted incidence rate for all childhood leukemias remained relatively stable in a sample of five geographic areas, changing from 4.6 per 100,000 children under 15 yr of age to 4.3 per 100,000. In contrast, the corresponding age-adjusted mortality rate fell approx 45% over the same period, from 4.4 per 100,000 to 2.4 per 100,000. (Author abstract) (32 Refs)

58. HYPOPLASTIC ACUTE LEUKEMIA.

Needleman SW, Burns CP, Dick FR, Armitage JO
Dept. Medicine, Univ. Iowa Hosp., Iowa City, IA, 52242
Cancer; 48(6):1410-1414 1981

There have been few reports of acute leukemia presenting with a hypocellular bone marrow. All patients diagnosed as having acute leukemia were identified during a recent 6-yr interval who had blast cells plus promyelocytes of greater than 30% and marrow cellularity of needle biopsy less than or equal to 50%. Of 195 patients analyzed, 15 (7.7%) fulfilled the criteria. Ten patients were men and 5 women; the median age was 68 yr with a range of 40-82. Seven complained of fatigue of 6-12 mo duration, five were seen with occult infection, and three were asymptomatic. Hepatosplenomegaly was absent in 93% and none had lymphadenopathy. Fourteen patients were pancytopenic with median WBC count at presentation of 1.5 x 10(9)/liter, Hb of 9.0 g/dl, and platelet count of 55 x 10(9)/liter. Circulating blast cells were not observed in 10 patients; in the other 5 they were less than 0.7 x 10(9)/liter. The morphology of all cases appeared myeloid and Auer rods were seen in three patients; however, in one the peroxidase was negative. Classification according to FAB criteria revealed 10 to be M1, 3 to be M2, 1 M4, and 1 L2. Median survival of the entire

group was 7 mo. Of seven patients receiving no chemotherapy, two survived longer than 1 yr (14, 24.5 mo), one is alive at 7+ mo, and the median survival was 7 mo. Eight patients with life-threatening complications received various combination regimens including an anthracycline, cytosine arabinoside, 6-thioguanine, vincristine, and prednisone. Five died of treatment complications; two achieved durable complete remission and are free of disease at 17 and 27 mo. It can be concluded that hypoplastic acute leukemia is a distinct nosologic entity affecting primarily older patients with myeloid leukemia. Remission induction therapy in patients who are seriously ill has a low success rate, and in some patients prolonged survival is possible with supportive care alone. (Author abstract) (19 Refs)

59. ACUTE LYMPHOBLASTIC LEUKEMIA IN SWEDISH CHILDREN 1973-1978.

Gustafsson G, Kreuger A, Dohlwitz A
Dept. Paediatrics, Univ. Hosp., S-750 14 Uppsala, Sweden
Acta Paediatr Scand; 70(5):609-614 1981

Three hundred and sixty-seven children with acute lymphoblastic leukemia have been diagnosed in Sweden 1973-1978, 345 of whom were treated according to the national uniform regimens of the Swedish Child Leukemia Group (SCLG). The patients were classified into an SR (standard risk) and an IR (increased risk) group. Remission was obtained in 354 patients (96%). With 12-84 mo observation time the total survival was 54% and the disease free survival 44%. A more intensive cytostatic regimen in the induction period increased considerably the disease free survival for SR and to some extent also for the IR patients. Relapses were significantly more common in the IR group in spite of a more intensive cytostatic regimen. The most decisive IR criteria were B-LPK and age at diagnosis. Prognosis was significantly worse for boys in all groups. After 3 yr in CCR treatment was discontinued in 95 out of 246 children (38%) of whom 19 later relapsed (20%). (Author abstract) (6 Refs)

60. CHARACTERISTICS OF CHILDREN WITH ACUTE NONLYMPHOCYTIC LEUKEMIA IN LONG-TERM CONTINUOUS REMISSION: A REPORT FOR CHILDRENS CANCER STUDY GROUP.

Baehner RL, Kennedy A, Sather H, Chard RL, Hammond D
Childrens Cancer Study Group Operations Office, 1721 Griffin Ave., Los Angeles, CA, 90031
Med Pediatr Oncol; 9(4):393-403 1981

Children and young adults less than 18 yr of age with acute nonlymphocytic leukemia who remained in long term bone marrow and extramedullary remission for two yr or longer since starting maintenance were compared to the remaining responders for the following characteristics: cell type, sex, age at diagnosis, race, pretreatment, white blood count, length of time from start of induction therapy to achievement of an M1 marrow, marrow rating at day 56 of therapy, marrow rating at the start of maintenance therapy, and specific study. Forty-eight patients of a group of 333 qualified as having long term remission (14.4%). Multivariant analysis indicated that patients between the ages of 3 and 10 yr ($p = 0.003$) as well as the length of time to achieve an M1 marrow from the start of treatment ($p = 0.03$) were the only characteristics associated with achievement of a long term remission. Maintenance therapy was discontinued in 15 patients from 2.5 to 4.8 yr after start of maintenance and all patients remained in bone marrow remission for periods from 0+ to 3.0+ yr after stopping treatment. Of the 33 who have remained on a continuous maintenance therapy 12 have had bone marrow relapses. These data confirm the prognostic value of age and length of time to achieve remission during induction in acute nonlymphocytic leukemia and suggest that there may be no significant benefit from maintenance therapy continued beyond 2 yr for patients in their initial remission. (Author abstract) (14 Refs)

61. LOW- AND HIGH-RISK NON-T NON-B AND T-CELL ACUTE LYMPHOID LEUKEMIA (ALL) IN CHILDHOOD: DIFFERENT DURATION OF REMISSION AND SURVIVAL.

Imbach P, Baumgartner C, Berchtold W, Gautier E, Gugler E, Hirt A, Morell A, Tonz O, Wyss M, Zurbrugg R, Wagner HP
Universitatskinderklinik Inselspital, CH-3010, Bern, Switzerland
Med Pediatr Oncol; 9(4):309-317 1981

In a prospective, nonrandomized trial clinical (initial WBC and chest film) and immunological (surface immunoglobulin and rosetting with pretreated sheep SRBC) criteria were used to stratify 69 children with previously untreated acute lymphoid leukemia (ALL). Forty of 61 evaluable patients had low risk (ALL) (initial WBC 20,000/mm3 or less, no mediastinal mass) and were treated less intensively. Twenty-one of 61 patients had high-risk ALL (initial WBC greater than 20,000/mm3 and/or mediastinal mass) and were treated more intensivy. Of the high-risk patients 15 had non-T non-B and 6 T ALL. Sixty of 61 patients went into complete remission. After a median observation period of 27 mo, 32 of 40 low-risk, 7 of 14 high-risk non-T non-B, and none of 6 high-risk T ALL patients were in continuous first remission. Thirty-six of 40 low-risk, 9 of 15 high-risk non-T non-B, and none of 6 T ALL patients were alive. Despite more intensive treatment, the duration of remission and the survival were significantly shorter in the high-risk than in the low-risk patients. Among the high-risk ALL, non-T non-B ALL did better than T ALL. (Author abstract) (33 Refs)

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DIAGNOSIS

1. MORPHOLOGICAL SUBSTRATE OF THE RADIOLOGICAL CHANGES OF THE DIGESTIVE TRACT IN LEUKEMIA.

Koval GJ, Zimonova ZN, Litvinova GS, Antonova RA, Gudim-Levkovich VV
Dept. Roentgenology, Kiev Inst. Postgraduate Training of Physicians, Dorogozhitskaia, 9, 252 112 Kiev, USSR
Radiol Diagn (Berl); 22(3):347-353 1981

The radiological and pathoanatomical findings in the digestive tract in leukemia were compared in 36 patients. The tumor-like exophytic and endophytic changes seen radiologi-

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cally were caused by local accumulations of leukemia cells, leukemia infiltrates, and by extravasal blood i n the mucosa and submucosa. The leukemic infiltration of the mucosa caused changes in the relief of the mucosa in the form of varying degrees of thickening of the folds. Swelling of the folds, rigidity, and reduced peristalsis were seen in the case of the infiltration of all layers, which appeared radiologically as endophytic growing carcinoma. It was not always possible to visualize radiologically ulcerative and necrotic processes. The involvement of the liver, spleen, and abdominal lymph nodes leads to displacements of the stomach and parts of the intestine. (15 Refs) (In GER)

2. THE DEVELOPMENT OF CEREBRAL CT CHANGES DURING TREATMENT OF ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDHOOD.

Pedersen H, Clausen N
Univ. Dept. Neuroradiology, Rigshospitalet, DK-2100 Copenhagen, Denmark
Neuroradiology; 22(2):79-84 1981

Twenty-three children with acute lymphocytic leukemia (ALL) were examined with cranial CT at least twice with a minimal interval of 10 mo. The first CT was performed at the time of diagnosis in 11 children and during therapy in 12; all but two were normal on the first CT examination. These two had slight enlargement of the ventricular system and subarachnoid space at the time of diagnosis. These findings were unchanged on the second CT examinations. Seven patients, all in remission from leukemia of the central nervous system manifested abnormal findings on later CTs. Low density areas in the periventricular white matter were seen in the brains of three, with increasing subcortical calcification in one of these cases. Five children had slight enlargement of the ventricular system and subarachnoid space, especially of the basal and Sylvian cisterns. Later CT examinations in five, plus brain autopsy in two cases, revealed unchanged or progressive conditions. The CT findings have been related to the treatment and some characteristics of the disease. The frequency of CT abnormalities was higher in patients who had received therapeutic irradiation and intraventricular methotrexate treatment. The possible reasons for the CT abnormalities are discussed. (Author abstract) (18 Refs)

3. CHILDHOOD ACUTE LEUKEMIA: A SEARCH FOR OCCULT EXTRAMEDULLARY DISEASE PRIOR TO DISCONTINUATION OF CHEMOTHERAPY.

Mahoney DH, Gonzales ET, Ferry GD, Sanjad SA, Von Noorden GK, Fernbach DJ
Res. Hematology Lab., Texas Children's Hosp., 6621 Fannin St., Houston, TX, 77030
Cancer; 48(9):1964-1966 1981

Between January 1978 and September 1979, 29 children with acute leukemia in complete continuous remission for 3 or more yr were examined for evidence of occult extramedullary disease immediately prior to discontinuation of chemotherapy. Bilateral open wedge testicular biopsy demonstrated the presence of bilateral leukemic infiltrates in 2/13 boys. Gallium scans prior to biopsy had identified unilatera l infiltration in an enlarged testis in one patient but failed to identify microscopic disease in the opposite testis or in the testes of the second patient. Percutaneous kidney and liver biopsies, pelvic ultrasonography, iv pyelogram, skeletal survey, cranial computed axial tomography scan, electroencephalography, and ophthalmologic examinations failed to demonstrate evidence of occult disease. Except for testicular biopsy, this study does not support extensive clinical or invasive procedures to identify extramedullary disease prior to discontinuation of chemotherapy. (Author abstract) (12 Refs)

4. CLINICAL SIGNIFICANCE OF BONE MARROW TREPHINE BIOPSY IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA.

Shardakov VI, Machul'skii LM
Inst. Blood Transfusion, Kirov, USSR
Probl Gematol Pereliv Krovi; 26(8):45-48 1981

The diagnostic efficacy of trephine biopsy was evaluated in 46 patients (25 men, 21 women; 15-69 yr) with chronic myeloid leukemia. Group I included 30 patients who were successfully treated with myelosan; av duration of disease was 33.9 mo. Group II included 16 patients in terminal stage of disease who did not respond to the treatment; av duration of the disease was 14.8 mo. Histological examination of bone marrow specimens showed fibrosis of the myeloid tissue in the patients from both groups, but the fibrotic changes were more pronounced in Group II. Development of myelofibrosis in the patients from Group II was associated with increased count of immature granulocytes and eosinophils. (5 Refs) (In RUS)

5. HISTOPATHOLOGY OF THE THYMUS OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA IN COMPLETE CLINICAL REMISSION.

Rappaport H, Machover D, Bearman R, Nathwani B, Lemaigre MG, Santelli G, Verley JM, Canon C, Mathe G
Dept. Anatomic Pathology, City of Hope Natl. Center, 1500 E. Duarte Road, Duarte, CA, 91010
Blood; 58(4):852-855 1981

The histologic features of thymuses from three patients who underwent thymectomy for acute lymphoblastic leukemia or lymphoblastic lymphoma in complete clinical remission are described. The thymuses from all three patients were fibrotic with a variability in the appearance of the lobules. Some of the lobules consisted predominantly of epithelial cells with small numbers of mature appearing lymphocytes, while other lobules were expanded and composed predominantly of cells having morphological features of immature lymphoid cells consistent with residual or recurrent disease. (Author abstract) (18 Refs)

6. RELATIONSHIP BETWEEN HISTOPATHOLOGY OF THE BONE MARROW AND CLINICAL STAGING IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Chelazzi G, Pinotti G, Bettini R, Michetti A
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Haematologica (Pavia); 66(2):187-195 1981

A retrospective study of 42 patients with chronic lymphoblastic leukemia, who underwent bone biopsy within 2 mo of diagnosis, was used to analyze the relationship between biopsy pattern and clinical stage according to Rai's classification. Histologic bone marrow result were arranged according to lymphocellular invasion on a quantitative and structural basis into the following types: forms with moderate lymphocyte accumulation of interstitial or nodular type, and forms with elevated lymphocyte accumulation of mixed or diffuse type. Statistically significant correlation was found between histopathologic aspects of bone marrow and clinical stage, expressing the progressive invasion of bone marrow from lower to higher accu-

mulation forms and associated prognostic meaning. (18 Refs) (In ITA)

7. PERIPHERAL DESTRUCTION OF PLATELETS IN CHRONIC LYMPHOCYTIC LEUKEMIA: RECOGNITION, PROGNOSIS AND THERAPEUTIC IMPLICATIONS.

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Am J Med; 71(4):729-732 1981

In patients with chronic lymphocytic leukemia and depressed platelet counts, it is important to discriminate between the thrombocytopenia due to bone marrow replacement with abnormal lymphocytes and that caused by increased peripheral destruction of platelets. The former is due to progressive chronic lymphocytic leukemia and, as a Rai Stage IV, carries a poor prognosis. The latter, as illustrated in four patients seen at the National Cancer Institute, may be remediable by either splenectomy alone or splenectomy followed by immunosuppressive and antitumor therapy. In all four patients, survival was substantially longer than for patients whose condition was classified as Rai Stage IV. The importance of identifying the subgroup of patients with chronic lymphocytic leukemia with reversible thrombocytopenia is emphasized by these examples. (Author abstract) (11 Refs)

8. THE PROGNOSTIC SIGNIFICANCE OF IN VITRO BONE MARROW GROWTH PATTERN IN ACUTE NON-LYMPHOCYTIC LEUKAEMIA.

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Scand J Haematol; 26(5):364-377 1981

The growth pattern of bone marrow cells in agar culture was studied in 56 patients with untreated acute non-lymphocytic leukemia. Four different growth patterns were recognized: (A) colony and cluster formation, (B) growth of small clusters (3-20 cells) only but less than 600/10(5) cells, (C) growth of small clusters only but more than 600/10(5) cells, and (D) no growth in vitro. Patients in Group A and B had a significantly higher remission rate (23/34) than patients in Group C and D (3/22). This was true also when only patients below 60 yr of age were considered. The median survival time of patients in Grou p A and B was 7.3 mo and 9.4 mo, and in Group C and D 4.0 mo and 3.3 mo. Identical growth patterns were found for marrow and blood cells in 21 of 27 patients studied and the number of clusters in blood and marrow showed a significant correlation ($r = +0.96$, p less than 0.001). The mean 3H-labelling index (LI) of myeloblasts determined in 32 patients was 14.8 +-7.8% (SD). Patients with LI below 15% tended to have a higher remission rate than patients with LI above 15%. It is concluded that the in vitro growth pattern at diagnosis of bone marrow cells from patients with ANLL is of value in detecting patients with a poor response to current therapeutic protocols. Such information could possibly lead to alternative cytostatic regimes in these patients. (Author abstract) (26 Refs)

9. MYELOID DYSPLASIA: THE HISTOPATHOLOGY OF PRELEUKEMIA.

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Haematol Blood Transfus; 26:34-37 1981

The presence of characteristic bone marrow lesions preceding obvious leukemia was studied. The similarity of these lesions in cases evolving into acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) was determined. Of 195 suspected preleukemia patients studied, biopsies of the bone marrow of 93 showed myeloid dysplasia. Of these 93 patients, 26 developed obvious leukemia during the course of the study. The results demonstrated that common morphological alterations exist in the bone marrow before onset of AML and CML and that they are associated with normochromic anemia and a slight to moderate pancytopenia of the peripheral blood count. The clinical as well statistical evaluation of our retrospective and prospective groups of patients confirms this statement. (14 Refs)

10. DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE CFU-C ASSAY IN ACUTE NONLYMPHOBLASTIC LEUKEMIA.

Mertelsmann R, Moore MA, Broxmeyer HE, Cirrincione C, Clarkson B
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer Res; 41(11,part2):4844-4848 1981

A simplified system for classification of aggregate incidence and growth pattern in the CFU-c (colony-forming units in culture) assay, allowing simple and reproducible interpretation of test results, was developed and applied to 552 bone marrow samples from 202 adult patients with acute leukemia. Ninety-six consecutive patients with acute nonlymphoblastic leukemia were studied at diagnosis. The microcluster growth pattern ('acute myeloid leukemia-type') found in 57% of the patients, was significantly associated with higher remission induction rates on both protocols ($p = 0.004$). No relationship between growth pattern at diagnosis and remission duration was observed. The acute myeloid leukemia-type growth patt ern was found to be more frequent in leukemias exhibiting morphological evidence for partial myeloid or monocytic differentiation. The favorable prognostic significance of Auer rods previously described was recognized in two CFU-c growth pattern categories. Of patients exhibiting an acute myeloid leukemia-growth pattern and Auer rods, 89% obtained complete remissions compared to 38% in the Auer rod-negative group showing other growth pattern variants. The CFU-c assays performed during complete remission on 354 samples of 48 patients with acute nonlymphoblastic leukemia and, as a control, on 85 samples of 43 patients with acute lymphoblastic leukemia revealed marked spontaneous as well as chemotherapy-related fluctuations of aggregate incidence and growth pattern. These and similar observations obtained with other assay systems are probably of major pathophysiological significance but preclude clinical application of the CFU-c assay to the monitoring of remission status in patients with acute nonlymphoblastic leukemia. (Author abstract) (31 Refs)

11. QUANTITATION OF CHEMOTHERAPY-INDUCED CYTOREDUCTION IN ACUTE LEUKEMIA.

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Haematol Blood Transfus; 26:73-76 1981

Results with a newly developed technique which allows the accurate quantitation of absolute number of cells/cubic mm (mm3) bone marrow (bm) are reported. The parameter was used to measured treatment-induced cytoreduction rate during induction therapy in 10 patients with acute non-lymphocytic leukemia (ANLL) and was also applied to a phase II study of high dose thymidine (TdR) therapy in 4 patients with end

stage acute leukemia and non-Hodgkin's lymphomas. In 9/10 ANLL patients, a total cell kill of 2.0-3.9 log10 of leukemic bm cells was measured during 5 days of therapy with daunorubicin, cytosine arabinoside, and thioguanine. In all nine patients, less than 5% blasts were found on bm examinations 1 wk after completion of chemotherapy. Six of nine patients subsequently experienced complete remission, two died in bm aplasia, and one developed early relapse 4 wk after completion of the first induction course. For three of the four patients with end stage acute leukemias and lymphomas, cell kill rates of 0.17, 0.13, and 0.13 log10/day were measured and all achieved bm aplasia as documented by bm biopsy. The fourth patient did not respond to TdR as judged by morphologic examination of bm aspirates and biopsies. The results indicated that quantitation of chemotherapy-induced cytoreduction by monitoring absolute number of leukemic cells/mm3 bm provides a new quantitative determinant for evaluating treatment efficacy in acute leukemia. Quantitation allows discrimination of responder from nonresponder and may become a determining progn ostic factor for remission duration. (12 Refs)

12. CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4838-4843 1981

Chromosome abnormalities in acute lymphoblastic leukemia (ALL) and their possible clinical significance are briefly reviewed based upon the literature and 60 cases studied at the University of Minnesota. Almost all cases of ALL appear to demonstrate clonal abnormalities; the major abnormal clone is usually hyperdiploid or pseudodiploid. Among cases of non-T, non-B ALL, at least four translocations appear to be present with an increased frequency: t(9;22); t(4;11); t(11;14); and t(1;3). Patients with these translocations appear to have unique clinical and laboratory findings. Although the presence of abnormal clones does not seem to influence remission duration, the nature of the abnormality does. Patients whose leukemias demonstrate predominantly a pseudodiploid abnormal clone or a translocation have significantly shorter first remissions. Most importantly, among patients with non-T, non-B ALL, the presence or absence of translocations may separate poor responders from good responders. (Author abstract) (42 Refs)

13. CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA: STRUCTURAL AND NUMERICAL CHANGES IN 234 CASES.

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(c/o A. Sandberg), Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(2):101-110 1981

Chromosomal abnormalities were found in cultured bone marrow and blood cells from 218/330 untreated patients and 16 treated patients with acute lymphoblastic leukemia. Five children and two adults (2.1% of the patients) had constitutional abnormalities, as opposed to 0.73% of 3,993 recently surveyed newborn infants. Of the 234 abnormal clones, 119 were pseudodiploid, 86 hyperdiploid, and 29 hypodiploid. Structural changes occurred in 204 cases, either alone (103) or combined with numerical changes (101); numerical changes alone accounted for 30 cases. The most common structural change was the presence of the Philadelphia chromosome associated with a translocation to chromosome 9. Chromosomes 1, 4, 6, 8, 11, and 14 also were involved in the structural changes. Lymphocyte marker studies in 182 cases showed that 72% were null cells, 19% T cells, and 9% B cells. Philadelphia chromosome-positive patients and those in the hyperdiploid category were all classified as having null cell leukemia. (8 Refs)

14. CLINICAL SIGNIFICANCE OF CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Mitelman F
(c/o A. Sandberg), Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(2):111-137 1981

Correlations between chromosome classification and clinical and hematologic findings at diagnosis, and the relation between karyotype and response to treatment, were examined in 173 adults and 157 children with acute lymphoblastic leukemia (ALL). All patients with a modal number greater than 46 and/or the Philadelphia chromosome had non-T-, non-B-cell ALL; children and adults with chromosome translocations and high initial WBC counts tended to have B-cell ALL. Patients with a normal karyotype or pseudodiploidy accounted for most of the T-cell ALL cases. The complete response rate to treatment was 91% for children and 65% for adults. ALL patients with a modal number greater than 50 responded best, and children in this group frequently appeared to be cured. Patients without chromosomal abnormalities or a 6q- also did well. In contrast, patients with t(4;11) or t(8;14) ALL responded poorly and had the shortest survival. Of the non-T, non-B ALL patients, those with a modal number less than 46 and the Philadelphia chromosome had the poorest prognosis and those with a modal number greater than 50, pseudodiploidy, or no abnormalities had the best prognosis. Karyotype was a prognostic variable independent of other risk factors such as age, WBC count, and FAB (Franco-American-British) classification. (4 Refs)

15. CORRELATIONS BETWEEN THE CLINICAL COURSE, CHARACTERISTICS OF BLAST CELLS, AND KARYOTYPE PATTERNS IN CHRONIC MYELOID LEUKEMIA.

Fleischman EW, Prigogina EL, Volkova MA, Frenkel MA, Zakhartchenko NA, Konstantinova LN, Puchkova GP, Balakirev SA
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Hum Genet; 58(3):285-293 1981

Correlations between karyotype and clinical and morphologic manifestations of chronic myeloid leukemia (CML) were studied. A cytogenetic study of 101 CML patients (87 adults; 14 children less than 16 yr old) was performed. The karyotype of 61 patients was analyzed in the terminal (acute) stage. Standard (9;22)(q34;q11), atypical (10;22), and complex translocations of the Philadelphia chromosome (Ph1) were observed in 95/101, 1/101, and 5/101, respectively. Only Ph1 translocations could be found in the leukemic cells of most of the patients in the chronic phase. Cell lines with some additional karyotype abnormalities were discovered in two patients. Additional chromosome abnormalities were discovered in 4/8 patients in the transitional stage. Cell clones with additional chromosome abnormalities were found in 47/61 terminal phase patients. These clones constituted 4-100% of the total number of cells, usually more than 50%. The chromosome changes in the acute phase of CML were nonrandom and usually involved pairs 8, 17, and 19. The terminal phase patients are divided into four groups according to the type of leukemic cell chromosome alteration; s ignificance of these alterations is discussed. (33 Refs)

16. CYTOMORPHOLOGY AND PROGNOSIS OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Vecchi V, Rosito P, Vivarelli F, Mancini AF, Pession A
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Haematologica (Pavia); 66(3):289-302 1981

A retrospective evaluation was made of the usefulness of the acute lymphoblastic leukemia (ALL) classification proposed by the French-American-British (FAB) cooperative group. FAB classification was adopted by the Children's Cancer Study Group, which added two transitional groups: L1/L2 and L2/L1, between L1 and L2, defined as percentages of cells with morphology L1 and L2. Using this enlarged classification, survival time and importance of morphology as a prognostic index were evaluated. Bone marrow blood smears of 79 patients (1-13 yr old; 43 male and 36 female) with ALL, receiving the same radio- and chemotherapy, were evaluated by four examiners separately and then together. At least 200 cells were counted in every case. Approx 70% of ALL patients had favorable morphology (L1, L1/L2), and 30% had morphology with unfavorable prognosis (L2, L2/L1). First complete remission curves of the two groups are significantly different. The prognostic value of leukemic lymphoblast morphology is especially evident in low risk patients with WBC less than 10,000/ml, 3-6 yr old. These three parameters can be used together to divide patients into different risk groups and to determine suitable therapy. (46 Refs) (In ITA)

17. CYTOCHEMICAL MARKERS OF DIFFERENTIATION IN ACUTE LEUKEMIA.

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Cancer Res; 41(11,part2):4824-4832 1981

Material from 110 adult patients with acute myeloid leukemia, acute lymphoblastic leukemia, and chronic granulocytic leukemia (CGL) in blast crisis (BC) was studied by light microscopy (LM) and transmission electron microscopy cytochemistry in order to examine the sensitivity of the tests used to define myeloid differentiation. Granulocytic differentiation was best visualized by the myeloperoxidase (MPO) reaction. By LM, the Hanker method using 3,3'-diaminobenzidine at pH 7.6 was the most sensitive in demonstrating MPO and the presence of phi bodies in most acute myeloid leukemias and some CGLs in 'myeloid' BC. Phi bodies were more numerous when the reaction was carried out at pH 9.7, suggesting that they originate from catalase-containing microperoxisomes. MPO at transmission electron microscope level (with 3,3'-diaminobenzidine) was more sensitive than the LM techniques because it demonstrated myeloblasts with few positive granules and reaction product in the endoplasmic reticulum. The platelet-peroxidase technique of Breton-Gorius, using a higher concentration of 3,3'-diaminobenzidine and unfixed material, was of even greater sensitivity for the study of myeloid precursors and allowed the identification of megakaryoblasts in CGL in BC. Monocytic differentiation was best recognized by LM using an esterase method (naphthol AS-acetate or alpha-naphthyl acetate) and the acid phosphatase reaction. By transmission electron microscopy, the acid phosphatase reaction was positive in small electron-dense granules which are MPO negative and appear to be characteristic of the early maturation stages of monoblasts. The techniques described were of value in the classification of CGL in BC and demonstrating the myeloid component in 8 of 56 (14%) acute myeloid leukemia cases which were positive with the enzyme terminal transferase. Five of the latter were 'pure' myeloid cell proliferations, and three others were 'mixtures' of lymphoblasts and myeloblasts (or monoblasts), but with lymphoid cells predominating in two of them. (Author abstract) (31 Refs)

18. LYMPHOBLASTIC LYMPHOMA/LEUKEMIA OF T-CELL ORIGIN: ULTRASTRUCTURAL, CYTOCHEMICAL, AND IMMUNOLOGIC FEATURES OF TEN CASES.

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Cancer; 48(9):1982-1991 1981

Ten cases of T-lymphoblastic lymphoma/leukemia were studied with light and electron microscopy. Cytochemical stains were performed on touch preparations, and mononuclear cell suspensions were tested for spontaneous rosette formation with sheep RBC, C3 receptors, and surface Ig. The present investigation was performed to evaluate several ultrastructural parameters, mainly the nuclear shape, as diagnostic clues for this group of lymphomas. Characteristic convoluted nuclei were present in 7 to 47% of the lymphoblasts. This percentage correlated with the focal acid phosphatase reaction and E-rosette formation. Acid phosphatase was the best cytochemical marker (7-100% of the lymphoblasts showed focal reaction product). By ultrastructural cytochemistry, the reaction product was demonstrated in the Golgi cisternae and primary lysosomes. The cell suspensions obtained from different sources contained 14 to 95% E-rosette-forming cells. No specific morphologic, cytochemical, or immunologic differences were found between patients with or without mediastinal involvement. (Author abstract) (63 Refs)

19. A CLINICAL AND LABORATORY EVALUATION OF 28 PATIENTS WITH HAIRY CELL LEUKEMIA.

Bernadou A, Pelletier G, Cadiou M, Giannoni F, James JM, Bilski-Pasquier G
Clinique Hematologique et Centre de Diagnostic, Hotel Dieu, 1, place du Parvis-Notre-Dame, 75181 Paris, France
Sem Hop Paris; 57(33-36):1361-1365 1981

Of 28 patients with hairy cell leukemia 5 were woman and 23 were men. Age ranged from 31 to 81 yr old. All patients except one presented with cytopenia, and 20/28 were pancytopenic. In 11/14 patients tested, tartrate-resistant acid phosphatase activity was positive. Bone marrow biopsy revealed myelofibrosis and leukemic infiltration in all patients. Isotope tests demonstrated hemodilution, hemolysis, and dyshematopoiesis in several patients. Immunological tests revealed various types of hypergammaglobulinemia in 15 patients, but there were no cases of hypogammaglobulinemia. Both T and B cells populations were lower in the blood of the majority of patients studied. In 12 patients whose spleen was removed because of pancytopenia, the levels of Hb, segmented cells, and thrombocytes were significantly higher after surgery. Median survival rate was 57 mo in the splenectomized group compared with 19 mo for the patients who did not undergo surgery. Bronchial and pulmonary infections were especially frequent, and the number of infections among splenectomized patients was lower. Death was caused by pancytopenia, infections and hemorrhage. More deaths occurred among the non-splenectomized group (9/14) than among the splenectomized group (5/14). (10 Refs) (In FRE)

20. CLASSIFICATION OF ACUTE LEUKEMIAS.

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Ann Biol Clin (Paris); 39(4):155-164 1981

Morphological, electron microscopic, immunologic, and chromosomal classifications of acute leukemias are discussed. Morphological classification is based on blood and bone marrow smears and on certain simple cytochemical reactions. According to this schema leukemia can be classified as acute lymphoblastic (L1, L2, or L3, Burkitt's type) and acute myeloblastic (without or with maturation, hypergranular promyelocytic, myelomonocytic, acute monocytic, and erythroleukemia, M1-6, respectively). Electron microscopic analysis permits the analysis of the fine structure of Auer bodies and allows the recognition of the myeloid (myeloblastic or megakaryocytic) nature of certain leukemias classified as lymphoblastic or undifferentiated on the basis of cytological or cytochemical findings. Immunologic study, using membrane markers, provides useful information for the classification of lymphoblastic leukemias as T-cell, B-cell, and non-T, non-B-cell leukemias. Biochemical tests utilizing lysozyme and terminal-deoxynucleotidyltransferase measurements are described. Karyotypic anomalies can also be associated with various forms of acute lymphoblastic or myeloblastic leukemia. (57 Refs) (In FRE)

21. CLINICAL UTILITY OF LEUKEMIA CELL TERMINAL TRANSFERASE MEASUREMENTS.

McCaffrey R, Lillquist A, Sallan S, Cohen E, Osband M
Section Medical Oncology, Evans Dept. Clinical Res., Univ. Hosp., Boston, MA
Cancer Res; 41(11,part2):4814-4820 1981

Interest in the DNA-synthetic enzyme terminal deoxynucleotidyl transferase (TdT) has developed from two sets of observations: first, in normal animals, it occurs only in immature thymic lymphocytes and in a subpopulation of bone marrow lymphocytes: second, it is present in the blast cells of almost of all patients with acute lymphoblastic leukemia. A prospective trial to evaluate blast cell TdT as a predictor of responsiveness to vincristine and prednisone in 30 Philadelphia chromosome-positive patients with blastic chronic myelogenous leukemia was undertaken. Eleven of 16 TdT-positive patients responded, whereas only 1 of 14 TdT-negative patients showed improvement. Among TdT-positive patients under the age of 50 yr, the response rate was 78%. Enzyme-negative patients under the age of 50 had an 11% response rate. Blast cell morphology (ie, lymphoblastic vs myeloblastic) had no significant correlation with either responsiveness or TdT activity. These results suggest that blast cell TdT activity may identify leukemic patients who are likely to respond to vincristine and prednisone irrespective of their conventional classification. (Author abstract) (49 Refs)

22. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY IN CHILDHOOD AND ADULT ACUTE LYMPHOBLASTIC LEUKEMIA.

Proctor SJ, Dickinson AM, Fail B, Walker W, Serisier S
Dept. Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, England
J Clin Pathol; 34(8):892-895 1981

The measurement of terminal deoxynucleotidyl transferase (TDT) activity in leukemic blasts of 26 cases of acute lymphoblastic leukemia (ALL) (13 children less than 14 yr, 13 adults greater than 14 yr) demonstrated significantly greater activities of the enzyme in a proportion of the adults. The predominant cytological sub-type in the adult patients was L2 (FAB classification) whereas L1 cytological sub-type dominated in the childhood group. There was no relation between TDT values and FAB sub-type but the highest activities in the childhood group were seen in patients assessed at the time of relapse. We conclude that continued use of quantitative TDT estimations may provide useful information in further characterizing the currently recognized cytological and immunological sub-types in ALL. (Author abstract) (9 Refs)

23. METHODS AND CLINICAL RELEVANCE OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE DETERMINATION IN LEUKEMIC CELLS.

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Haematol Blood Transfus; 26:68-72 1981

Current technology for the demonstration of terminal deoxynucleotidyl transferase (TdT) is reviewed. The significance of TdT in the clinical and pathophysiologic evaluation of human leukemias and lymphomas is discussed. In acute leukemias, the highest levels of TdT activity are found in approx 95% of non-T, non-B, and T cell acute lymphoblastic leukemias. Elevated levels of TdT have also been observed in some patients with acute nonlymphoblastic leukemia. All myeloproliferative syndromes (MPS: polycythemia vera and chronic myeloid leukemia) and myelodysplastic syndromes (MDS) were found to be TdT- during the chronic phase of their disease; approx 30% of blast phase chronic myeloid leukemias and 15% of other MDS and MPS terminating in acute leukemia were found to exhibit high levels of TdT activity. In patients with lymphoblastic lymphomas of the T and null cell type, high levels of TdT were observed. Lymphoproliferative diseases of the mature T and B cell type have been found to be TdT-. The significance of TdT markers for diagnosis, therapy planning, and prognosis is discussed. The relationship of TdT determinations to monitoring of disease activity in TdT+ neoplasia is considered. The determination of TdT activity and definition of cell phenotypes in hematopoietic malignancies may be useful tools for classification of these disorders and may have significant prognostic, clinical, and pathogenetic implications. (17 Refs)

24. CYTOCHEMICAL DEMONSTRATION OF 5-FORMYL-TETRAHYDROFOLATE CYCLODEHYDRASE ACTIVITY IN LEUCOCYTES OF PATIENTS WITH ACUTE LEUKAEMIA.

Tzortzatou-Stathopoulou F, Zannos-Mariolea L, Karayiannis P, Pallis I, Matsaniotis N
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Scand J Haematol; 26(5):393-397 1981

The activity of 5-formyl-tetrahydrofolate cyclodehydrase has been studied cytochemically in WBC of children with acute leukemia. Comparison of enzymatic activity in the same types of cells showed no significant variation between normal controls and the patients with acute leukemia. The blast cells were weakly positive or negative. This finding is of interest as the blast cells are capable of division. Probably the enzyme appears in the blast cells at some stage of the cell cycle. Two populations of lymphocytes were observed, one positive with a few granules and one negative. A reduction of enzyme activity was observed after prophylactic cranial irradiation and metho-

trexate decreased enzyme activity in some patients. (Author abstract) (11 Refs)

25. GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY AND REDUCED GLUTATHIONE LEVEL IN THE ERYTHROCYTES OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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Acta Haematol Pol; 12(2):85-89 1981

The glucose-6-phosphate dehydrogenase (G-6-PDH) activity and reduced glutathione (RG) level of erythrocytes were studied in children (2.5-13 yr old) with acute lymphoblastic leukemia. Ten healthy children of the same age group were used as controls. Both the G-6PDH activity and the RG level were appreciably but insignificantly elevated in the patients compared with the controls before the therapy, and they were increased significantly compared with both the controls and the pre-therapy values during remission achieved by polycnemotherapy. The G-6-PDH activity and RG level returned to the normal range 5-24 mo after the end of the chemotherapy. (18 Refs) (In POL)

26. LEVEL OF CATION PROTEINS IN MYELOID CELLS OF HEALTHY CONTROLS AND PATIENTS WITH ACUTE AND CHRONIC MYELOID LEUKEMIA.

Protsenko VA, Shpak SI, Kritenko GI
Dept. Physiopathology, Crimean Medical Inst., Simferopol, USSR
Probl Gematol Pereliv Krovi; 26(8):54-56 1981

The content of nonenzymatic cation proteins was studied in the myeloid cells from 5 healthy controls, 10 patients with chronic myeloid leukemia (CML), and 10 with acute myeloid leukemia (AML). Compared with healthy controls, the patients with CML and AML showed significant increase of the number of promyelocytes and granulocytes with low content or absence of cation proteins. (3 Refs) (In RUS)

27. INCREASED ASCORBIC ACID CONTENT IN CHRONIC LYMPHOCYTIC LEUKEMIA B LYMPHOCYTES.

Liebes L, Krigel R, Kuo S, Nevrla D, Pelle E, Silber R
Dept. Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Proc Natl Acad Sci USA; 78(10):6481-6484 1981

Human lymphocyte extracts analyzed by high-performance liquid chromatography reveal a major UV-absorbing peak that was shown to be ascorbic acid by spectral, chemical, and enzymatic criteria. Because this peak appeared very prominent in the elution profile of chronic lymphocytic leukemia (CLL) lymphocyte extracts, we measured the ascorbic acid content in lymphocytes from the blood of normal subjects and untreated patients with chronic lymphocytic leukemia. A significantly higher concentration of 111 +-15.3 nmol per 10(8) cells (mean +- SEM) was found in CLL lymphocytes than in normal blood lymphocytes, which contained 42.2 +-3.3 nmol per 10(8) cells. Selective enrichment with B and T cells showed that this difference was limited to the chronic lymphocytic leukemia B cell, which had 5-to 15-fold higher content of ascorbic acid than normal B cells had. In contrast, the ascorbic acid level was similar in normal and CLL T cells. The very high ascorbic acid content provides the chronic lymphocytic leukemia B cell with a reducing substance that could react with oxidants or free radicals. (Author abstract) (29 Refs)

28. EVALUATION OF DIAGNOSTIC SIGNIFICANCE OF PLASMA AND LEUKOCYTE LYSOZYME IN HUMAN LEUKAEMIA.

Seshadri KN, Baxi AJ
Cancer Res. Inst., Parel, Bombay 400 012, India
Indian J Cancer; 18(3):188-193 1981

Plasma and leukocyte levels of lysozyme (muramidase) were studied as a diagnostic marker in 193 subjects. Cases included 53 normal controls and 140 patients with various types of leukemia. Morphologic diagnosis was based on a thorough histologic and cytochemical examination. Significant elevation of plasma lysozyme (PL) was found in 53-63% of cases involving chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute myelomonocytic leukemia (AMML), or CML with myelofibrosis. Normal PL values were found in cases of acute promyelocytic leukemia (APML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), or acute lymphosarcoma (ALS). Leukocyte lysozyme (LL) levels were 3-12 ug/mg protein in controls. LL values for CML, AML, CLL, ALL, AMML, and HCL were greatly increased (56-105 ug/mg protein). PL/LL ratios were generally higher in chronic and acute lymphatic leukemia patients than in myeloid leukemia patients. No linear relationship between PL and LL in individual cases was found. PL values could not be used to differentiate granulocytic from lymphocytic leukemias. (20 Refs)

29. PURINE PATHWAY ENZYME ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4821-4823 1981

The status of three purine pathway enzymes, adenosine deaminase, 5'-nucleotidase, and purine nucleoside phosphorylase, was evaluated in the leukemic cells of patients with acute lymphoblastic leukemia and correlated with routine immunological cell surface markers. A distinct pattern of enzyme activity was noted in T-lymphoblasts which have significantly higher adenosine deaminase activity (p less than 0.02) and lower 5'-nucleotidase (p less than 0.001) and purine nucleoside phosphorylase (p less than 0.01) activities than do non-T, non-B lymphoblasts. This enzyme pattern is similar to that observed in normal human thymocytes but is not shared by the mature, normal T-lymphocytes of peripheral blood, suggesting that it may reflect the differentiation status of malignant T-lymphoblasts. These findings, which confirm the biochemical heterogeneity of acute lymphoblastic leukemia, may provide an avenue for selective chemotherapy of this disease. (Author abstract) (19 Refs)

30. CHEMICAL CHARACTERIZATION OF NEUTRAL GLYCOLIPIDS IN HUMAN MYELOID LEUKEMIAS.

Klock JC, D'Angona JL, Macher BA
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J Lipid Res; 22(7):1079-1083 1981

Human neutrophils and lymphocytes have been shown to have different classes of neutral glycolipids. We have investigated alterations of glycolipids in the human myeloid leukemias to see how their neutral glycolipids differ from those of normal neutrophils. The chemical structures of the neutral glycolipids from large numbers of homogeneously purified leukemia cells were determined using column and thin-layer chromatography, gas-liquid chromatography (GLC), GLC-mass

spectrometry, and direct probe mass spectrometry. Our results showed that cells from patients with acute myelogenous leukemia (AML) had less than half the amount of neutral glycolipid per cell than did cells from patients with chronic myelogenous leukemia (CML). Chromatographic mapping of the neutral glycolipids from these cells showed that AML cells had less of the polar, long-chain neutral glycolipids than did CML cells. The studies confirmed that over 99% of the neutral glycolipids were contained in a population of compounds with 1, 2, 3, and 4 sugar-containing neutral glycolipids. Lactosyl ceramide was the major glycolipid in both AML and CML cells. The studies show that human myeloid leukemia cells have the same neutral glycolipids as normal neutrophils. The alterations in neutral glycolipid distribution in leukemia suggest that they might be useful as 'differentiation markers', with the morphologically more 'mature' leukemias having more complex glycolipids. We were unable to detect novel or 'malignancy-associated' neutral glycolipids in any of the leukemias we studied. (Author abstract) (15 Refs)

31. HAEMOGLOBIN AND PROGNOSIS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA.

Hann IM, Scarffe JH, Palmer MK, Evans DI, Jones PH
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Arch Dis Child; 56(9):684-686 1981

Two hundred and nine children presenting consecutively with acute lymphoblastic leukemia to a regional pediatric oncology unit were investigated to determine the prognostic significance of various factors at diagnosis. There was a strong positive correlation between the pretreatment Hb level and the percentage of bone marrow blast cells in S phase of the cell cycle as assessed by flow cytometry. Patients with T- and B-cell leukemia had significantly higher Hb levels than non-B non-T patients. In patients with total white cell counts less than 20 x 10(9)/l, aged less than 13 yr, and no mediastinal mass, there was no association of Hb with length of first remission. However, among those with white blood counts greater than 20 +-10(9)/l there was a strong positive trend towards shorter remission with higher Hb levels. Children with high white blood counts at diagnosis and low Hb levels may have a better prognosis than predicted by the white blood count alone. (Author abstract) (17 Refs)

32. GLUCOCORTICOID RECEPTORS AND IN VITRO RESPONSES TO GLUCOCORTICOID IN ACUTE NONLYMPHOCYTIC LEUKEMIA.

Crabtree GR, Bloomfield CD, Smith KA, McKenna RW, Peterson BA, Hildebrandt L, Munck A
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Cancer Res; 41(11,part2):4853-4856 1981

Early clinical studies in which glucocorticoids were used alone in the treatment of acute nonlymphocytic leukemia (ANLL) reported a wide range of responses from remission in some patients to dramatic aggravation of the disease in others. In the hopes of identifying those patients likely to derive therapeutic benefit from glucocorticoids, we have studied glucocorticoid receptors and in vitro responses to glucocorticoids in 36 previously untreated adults with ANLL. The leukemic blasts of all patients contained glucocorticoid receptors (range, 4,300 to 28,400 total receptor sites per cell; median, 8,800). These receptors were similar in all respects studied to those from a variety of other normal and malignant tissues. There was little difference between receptor levels among the various French-American-British categories. In vitro responses to glucocorticoid were observed in leukemic blasts of 26 of 28 cases studied. These responses varied from near complete cell killing to stimulation of proliferation. Since the cells of patients with ANLL have about the same number of receptors as do cells from patients with acute lymphoblastic leukemia and these receptors are capable of mediating physiological responses in vitro, it is unlikely that qualitative or quantitative receptor defects underlie the relative resistance to glucocorticoid therapy of ANLL compared to acute lymphoblastic leukemia. However, the broad range of in vitro responses and receptor levels suggests that these studies might be useful in identifying those patients with ANLL likely to derive benefit from steroid therapy. (Author abstract) (23 Refs)

33. A CLINICAL PERSPECTIVE ON CELL MARKERS IN ACUTE LYMPHOCYTIC LEUKEMIA.

Bowman WP, Melvin SL, Aur RJ, Mauer AM
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Cancer Res; 41(11,part2):4794-4801 1981

Two hundred consecutive new patients, with acute lymphocytic leukemia (ALL) have been studied with a battery of five cell marker assays to determine if a classification system with prognostic significance can be developed; 182 have been classified among four groups as follows: 33 T-cell, 3 B-cell, 126 common, and 20 undifferentiated ALLs. Patients with T-cell disease are likely to have unfavorable clinical prognostic features and a poor response to therapy. Rare patients with B-cell disease are closely related clinically to non-Hodgkin's lymphoma. Those with common ALL infrequently have unfavorable clinical features and have a superior outcome to that of T-cell patients. Children with undifferentiated markers seem to respond less well to treatment than do those with common ALL, yet may not be identifiable as poor risk by clinical features. What remains to be resolved with further observation is whether these marker patterns are more reliable indicators of prognosis than the usual clinical determinants predisposing to treatment failure (high WBC count, mediastinal mass, and CNS disease). At the present time, it appears that in the absence of poor-risk clinical prognostic features, patients with common ALL are more likely to have lasting remissions than those with RBC-rosette-positive T-cell disease or those with ALL that is undifferentiated by markers. (Author abstract) (9 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

34. CLASSIFICATION OF HUMAN LEUKEMIA BY MEMBRANE ANTIGEN ANALYSIS WITH XENOANTISERA.

Metzgar RS, Dowell BL, Lachman LB, Jones NH, George FW
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Cancer Res; 41(11,part2):4781-4785 1981

Rabbit and monkey antisera after appropriate absorption were rendered specific for normal or leukemic lymphoid- and myeloid-associated antigens. Antisera defining a common peripheral blood T-cell antigen, a thymus leukemia antigen, HLA-DR or Ia-like antigen (CALLA) common acute lymphoblastic leukemia antigen, and a myeloid-monocyte (M) anti-

gen were used in a microcytotoxicity assay to classify leukemic cells from 30 patients in a double blind study. The antisera to the M antigen reacted with adherent peripheral blood cells and polymorphonuclear leukocytes and failed to react with nonadherent mononuclear cells and enriched T-cells and chronic lymphocytic leukemia cells. The M antisera also reacted with U937, a monocytic-type cell line, and with HL60, a promyelocytic-type cell line, but failed to react with T and B lymphoblastoid cell lines. The specificities of the other antisera have been described in previous reports. Cells from three of the patients could not be phenotyped by microcytotoxicity testing. Cells from 25 patients had a consensus morphological or histochemical diagnosis of either acute lymphoblastic leukemia or acute nonlymphocytic leukemia. The serological classification of these patients using the five types of antisera listed above were consistent with the consensus diagnosis. In addition, the lymphoid cancers were further sub-classified as to T-, B-, or thymus antigen types. There was no consensus lymphoid versus myeloid diagnosis on cells from two patients. The serological classification in both cases favored a diagnosis of myeloid rather than lymphoid leukemia. (Author abstract) (20 Refs)

35. BIOCHEMICAL CHARACTERIZATION OF AN ANTIGEN ASSOCIATED WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOCYTE PRECURSORS.

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Haematol Blood Transfus; 26:326-328 1981

An antigen (ALLA) occurring on the surface membrane of cells from patients with common acute lymphoblastic leukemia (ALL) was previously identified. ALLA was also found in some cases of undifferentiated leukemias and chronic myeloid leukemia and in a small proportion of normal bone marrow cells. ALLA from the cell line Nalm-1 was characterized biochemically. ALLA is a glycosylated polypeptide of approx 100,000 daltons. No intrachain disulfide linkages are present. ALLA shows 50% binding with lentil lectin, but 100% binding with Ricinis communis lectin. Lectin binding and nonbinding forms form identical homogeneous spots in two-dimensional isoelectric focusing with a pI of 5.1-5.5. Neuraminidase treatment of both forms causes a shift of approx 0.6 towards the basic end of the gel. Treatment with tunicamycin and glycosidases indicate that up to 25% of ALLA mol wt may be carbohydrate, but carbohydrate is not involved in the antigenic site. ALLA is apparently not integral to the cell membrane, but is closely associated with it. Presence of ALLA in some normal bone marrow cells suggests the antigen is a normal product reflecting target cells for malignant transformation and/or the stage of maturation arrest of ALL cells. (11 Refs)

36. ACUTE MYELOBLASTIC LEUKEMIA-ASSOCIATED ANTIGENS: DETECTION AND CLINICAL IMPORTANCE.

Baker MA, Roncari DA, Taub RN, Mohanakumar T, Falk JA
No affiliation given
Haematol Blood Transfus; 26:332-337 1981

An analysis of material released into the supernatant medium of cultured myeloblasts of patients with acute myeloblastic leukemia was performed. Leukemia myeloblasts labeled with the lactoperoxidase 125I iodination technique released soluble compounds into the culture media that reacted immunologically with alloantisera to leukemia-associated antigens. Antisera raised in monkeys to compounds eluted from a diethylaminoethanol column were used to raise heteroantisera in monkeys that were selectively reactive with leukemic myeloblasts and unreactive with nonleukemic cells. Further study of compounds eluted from gel columns were applied to isoelectric focusing (pI). Fractions obtained were analyzed for reactivity by coprecipitation with the heteroantisera. Analysis of the immune precipitate of a major reactive peak at pI 7.8 yielded a homogeneous peak with a mol wt between 70,000 and 80,000 daltons. Sera from patients with acute myeloblastic leukemia significantly inhibited the reactivity of the heterosera, suggesting the soluble leukemic antigen is released in vivo as well. (28 Refs)

37. CELL SURFACE MARKERS AND KINETIC FEATURES IN ACUTE LYMPHOBLASTIC LEUKAEMIA.

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Haematologica (Pavia); 66(4):419-425 1981

The labelling index (LI) of cell surface antigen SM+ and SM- blast cells from 15 patients (11 children: 7 males, 4 females; 2-11 yr old; 4 adults: 3 men, 1 woman; 23-37 yr old) with acute lymphoblastic leukemia (ALL) and from 1 patient with chronic myelocytic leukemia (CML) in lymphoid-like blast crisis was examined. In the four cases of SM+ ALL studied (3 T-cell ALL and 1 B-cell ALL), the LI of bone marrow blasts was 9.47 +-3.90 (range 6.1-16.7) compared with 1.38 +-1.19 (range 0.6-4.0, p less than 0.01) in the 11 cases of ALL without conventional T and B markers. Cells from the patient in a lymphoid-like blast crisis of CML had a bone marrow LI of 5.7. Upon combined immunofluorescent and autoradiographic analysis of bone marrow blasts, SM+ blast always displayed LI values significantly higher than SM- blasts. The data indicated that in acute leukemia blast cell populations, SM+ and SM- blasts have different LI. The relationship of this phenomenon to the problems of blast proliferation and differentiation are discussed. (16 Refs)

38. COMPARATIVE ANTIGENIC PHENOTYPES OF NORMAL AND LEUKEMIC HEMOPOIETIC PRECURSOR CELLS ANALYSED WITH A 'LIBRARY' OF MONOCLONAL ANTIBODIES.

Greaves MF, Robinson JB, Delia D, Ritz J, Schlossman S, Sieff C, Goldstein G, Kung P, Bollum FJ, Edwards PA
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Haematol Blood Transfus; 26:296-304 1981

Antigenic phenotypes of normal and leukemic hemopoietic precursor cells were compared using a surface protein associated with common acute lymphoblastic leukemia (cALL), the gp 28/33 Ia-like or HLA-DR antigens, and a number of monoclonal antibodies. About 33% of cALL cells have a pre-B cell phenotype. Most have no mature T or B cell markers, and presumably represent hemopoietic precursor cells in maturation arrest. Leukemic cells also have the nuclear enzyme TdT. The cALL antigen and TdT have been found in a small number of normal lymphoid cells in bone marrow. These cells appear to have the same surface phenotype as cALL cells, indicating that cALL cells may not have leukemia-specific surface markers. The cellular expression of HLA-DR antigen in leukemic cells is matched by its expression on hemopoietic progenitor cells of myeloid and erythroid lineages. Surface phenotype of leukemic cells appears to reflect the stage of maturation at which they were arrested, rather than a leukemia-specific form.

How closely leukemic phenotype corresponds to normal developmental phenotype is, however, uncertain. (59 Refs)

39. DERIVATION OF HUMAN T-CELL LEUKEMIAS.

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Cancer Res; 41(11,part2):4767-4770 1981

Cell surface antigenic changes occur during the stages of T-cell ontogeny in several animal model systems. In the present study, multiple monoclonal antibodies were developed to human thymoc yte and T-cell surface differentiation antigens as a means of probing T-cell ontogeny in humans. It was shown that three distinct stages of human intrathymic differentiation exist and that the mature inducer (T4+) and suppressor (T5+/TH2+) T-cell subsets arise at specific points during these maturation events. Moreover, T-cell leukemias can now be related to the three stages of the thymic compartment or, alternatively, the more differentiated peripheral T-cell compartment. (Author abstract) (28 Refs)

40. IMMUNOLOGICAL DEFINITION OF LEUKEMIC CELL SURFACE PHENOTYPES.

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Cancer Res; 41(11,part2):4790-4793 1981

Immunological phenotyping of blasts from over 200 children with acute lymphocytic leukemia (ALL) reveals both interpatient differences and phenotypic heterogeneity in the blast population from individual patients. A battery of five independent lymphocyte differentiation markers, RBC-forming rosettes, T-cell antigens, Ia-like antigens, the common ALL antigen, and surface Ig, permit classification of all ALL specimens into four major marker groups. These are common, T-cell, B-cell, and undifferentiated ALL. Heterogeneity in the marker phenotypes within each of the major groups is observed. Within individual RBC receptor-positive ALL specimens, phenotypic heterogeneity in the blast population is demonstrated. Sequential determinations of the blast phenotype during periods of active disease reveal a second example of intrapatient blast cell heterogeneity. Differences in phenotype of the dominant blast populations present prior to treatment and at relapse are observed in sequential studies of individual patients. These shifts in phenotype are nonrandom. They result most frequently from losses in single differentiation markers. A unifying hypothesis which explains these observations of phenotypic heterogeneity is that ALL blasts manifest limited lymphoid-like differentiation. (Author abstract) (8 Refs)

41. SOUTHWEST ONCOLOGY GROUP EXPERIENCE WITH IMMUNOLOGICAL PHENOTYPING IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDHOOD.

Pullen DJ, Falletta JM, Crist WM, Vogler LB, Dowell B, Humphrey GB, Blackstock R, Van Eys J, Cooper MD, Metzgar RS, Meydrech EF
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Cancer Res; 41(11,part2):4802-4809 1981

The Pediatric Division of the Southwest Oncology Group is attempting to define subgroups of acute lymphoblastic leukemia (ALL) by laboratory delineation of marrow lymphoblast characteristics at diagnosis. Immunological subclassification studies include erythrocyte-forming rosette (E-rosette), C3 receptor, Fc receptor, surface Ig (Sig) and cytoplasmic Ig (CIg) determinations, as well as peripheral T (PT), thymocyte, Ia, and common ALL membrane antigen testing. Four subgroups of ALL have thus far been defined: null (SIg-, CIg,-, PT-); pre-B (SIg-, CIg+, PT-); B-cell (SIg+, CIg-, PT-); and T-cell (SIg-, CIg-, PT+). A group of 118 patients have had complete testing, and an additional 121 patients have had partial testing. Thirty-five patients with pre-B ALL and 27 patients with T-cell ALL have thus far been studied. Pre-B and null types of ALL appear closely related in multiple subclassification parameters (age, sex, physical findings, WBC count, and lymphoblast Ia and common ALL antigen positivity). Pre-B ALL patients treated with the same treatment regimens as were null ALL patients appear to have shorter durations of complete remission, although the difference has not yet reached statistical significance. Results suggest that the male predominance and older age distribution previously recognized for E-rosette-positive T-cell leukemia can also be expected in the E-rosette-intermediate and E-rosette-negative T-cell ALL subsets, although statistically higher WBC counts at diagnosis are seen in the E-rosette-positive subset. Mediastinal mass at diagnosis is most likely in the patient with E-rosette-positive, thymocyte antigen-positive lymphoblasts. The E-rosette intermediate and E-rosette negative, as well as the E-rosette positive, T-cell ALL subsets appear to constitute poor prognosis categories. Correlation with treatment results is preliminary in all groups but suggests that stratification of ALL at diagnosis according to several immunological subgroupings may prove helpful in planning therapy. (Author abstract) (32 Refs)

42. RELEVANCE OF SURFACE MARKERS IN CHRONIC LYMPHOCYTIC LEUKEMIA TO ACUTE LYMPHOCYTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4810-4813 1981

The surface membrane of the B-lymphocyte of chronic lymphocytic leukemia (CLL) has been subject to detailed investigation over the past decade. Surface Ig of low density, punctate in distribution, without the tendency to polar cap formation, and clonal with respect to light and heavy chains, is characteristic. Other B-cell properties include the presence of the Ia antigen and the receptor for the C3d portion of complement. The CLL surface membrane lacks such T-cell attributes as the ability to form rosettes with sheep RBC and reactivity with anti-T-cell antisera, although T-cells may be increased early in the disorder. CLL is believed to be a proliferation of a B-lymphocyte of the medullary cord of the lymph node, although the exact place of this cell in lymphocyte development remains to be clarified. Surface markers are useful in distinguishing classical B-cell CLL from other proliferations of small lymphocytes (lymphosarcoma cell leukemia of follicle-center B-cells, T-cell CLL, Sezary syndrome, and reactive lymphocytosis). (Author abstract) (36 Refs)

43. ANALYSIS OF THE CLINICAL AND BIOLOGICAL SIGNIFICANCE OF LYMPHOID PHENOTYPES IN ACUTE LEUKEMIA.

Greaves MF
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Cancer Res; 41(11,part2):4752-4766 1981

Analysis of leukemia cell phenotypes using cell surface antigens and various enzymes indicates that acute lymphoblastic

leukemia (ALL) is a biologically heterogeneous disease consisting of four major subclasses with additional subsets existing within these subclasses. These different types of ALL appear to reflect sequential stages of early lymphocyte ontogeny. There is a strong association between cell phenotype and first remission duration in ALL (p trend less than 0.0001) and an equally strong correlation between remission duration and WBC count at presentation. If common ALL and thymic ALL (T-ALL) are compared after adjustment of WBC counts, then the prognostic differences between these two major subclasses almost disappear ($p = 0.38$). It is suggested, therefore, that an immunological (and enzymatic) phenotype of ALL subclasses may not be an independent correlate of prognosis but nevertheless is linked to other differentiation-linked features, especially growth rate and sites of clonal expansion (eg, marrow versus thymus), which critically influence the size of the clonogenic leukemic population and its associated evolutionary status with respect to drug-resistant mutants at the time of diagnosis and introduction of therapy. An extensive library of monoclonal antibodies has been used to further define the phenotypic heterogeneity of T- and non-T ALL. Several of the antigenic structures identified by these monoclonal antibodies have been isolated and characterized. T-ALL can be dissected into several subsets - corresponding to stages of intrathymic differentiation. Non-T ALL (null-ALL, common ALL, and B-ALL) all have a phenotype indicative of B-lineage affiliation indicating that 'non-T, non-B' ALL may originate from B-cell precursors in bone marrow. A cell type is identified in normal bone marrow which has the same identical monoclonal antibody-defined phenotype as common ALL and may provide the target cell for this disease. (Author abstract) (94 Refs)

44. DEFINITION OF THE HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA PATIENT BY IMMUNOLOGICAL PHENOTYPING WITH MONOCLONAL ANTIBODIES.

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Cancer Res; 41(11,part2):4786-4789 1981

An accurate method of classification of the surface membrane characteristics of blast cells from patients with acute lymphoblastic leukemia would allow a more definitive study of the nature of this disease. Monoclonal antibodies have been produced to the surface antigens of leukemic bla sts from a patient with high-risk acute lymphoblastic leukemia. Two antibodies of interest were obtained from this immunization. These two, in combination with a monoclonal antibody with anti-Ia specificity, have been used to obtain surface phenotypes for patients with childhood acute lymphoblastic leukemia. Preliminary results indicate that the definition of a high-risk group, using these antibodies, is possible. (Author abstract) (16 Refs)

45. USE OF MONOCLONAL ANTIBODIES AS DIAGNOSTIC AND THERAPEUTIC REAGENTS IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Ritz J, Pesando JM, Notis-McConarty J, Clavell LA, Sallan SE, Schlossman SF
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Cancer Res; 41(11,part2):4771-4775 1981

A monoclonal antibody specific for a common acute lymphoblastic leukemia (ALL) antigen has been generated and characterized. This antibody (J-5) is reactive with leukemic cells from most patients with non-T-cell ALL and some patients with chronic myelocytic leukemia in blast crisis. J-5 antibody is not reactive with leukemic cells from patients with either T-cell ALL, chronic lymphocytic leukemia, acute myeloblastic leukemia, or stable-phase chronic myelocytic leukemia. In addition to diagnostic applications, anti-common ALL antigen monoclonal antibody has been used to study the effect of specific serotherapy in the treatment of ALL. In the first patient with ALL treated with J-5 antibody, a 90% reduction in circulating lymphoblasts occurred within 1 hr of starting antibody infusion. Despite continued serotherapy, however, lymphoblasts persisted in peripheral blood and bone marrow. Analysis of cell surface markers during serotherapy suggested that resistance to antibody-mediated lysis in vivo may have been due to antigenic modulation of leukemic cells in response to J-5 monoclonal antibody. (Author abstract) (27 Refs)

46. USE OF MONOCLONAL ANTIBODIES, MORPHOLOGY, AND CYTOCHEMISTRY TO PROBE THE CELLULAR HETEROGENEITY OF ACUTE LEUKEMIA AND LYMPHOMA.

LeBien TW, McKenna RW, Abramson CS, Gajl-Peczalska KJ, Nesbit ME, Coccia PF, Bloomfield CD, Brunning RD, Kersey JH
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Cancer Res; 41(11,part2):4776-4780 1981

A combined immunological, morphological, and cytochemical approach to the study of malignant cells in patients with acute leukemia and lymphoma is presented. Newly produced monoclonal antibodies that bind to antigens of human mononuclear cells (TA-1), or B-lymphocytes (BA-1) were used to study malignant cells from patients with acute lymphoblastic leukemia (ALL), acute myelocytic leukemia, acute myelomonocytic leukemia, and chronic lymphocytic leukemia. Results in lymphoid leukemia-lymphoma patients were compared with other immunological markers and indicate that the major groups of ALL and childhood no n-Hodgkin's lymphoma are T-ALL, pre T-ALL, pre-B-ALL, and non-T, non-B-ALL. In addition, each major group had multiple phenotypes when analyzed with seven immunological markers including the RBC rosette receptor, surface Ig, cytoplasmic Ig M, the early lymphocyte-acute lymphoblastic leukemia antigen, monoclonal antibody TA-1, monoclonal antibody BA-1, and a monoclonal antibody against HLA-Dr. While immunological heterogeneity was demonstrable within each group, distinct biological behavior was observed, with T-ALL and B-ALL generally presenting as 'lymphomas' and the others presenting as 'leukemias.' Morphological analysis using the French-American-British classification provided independent information in the definition of groups with differing clinical behavior. Cytochemical analyses demonstrated focal paranuclear staining of leukemia cells with acid phosphatase in 73% of T-ALLs and 6% of non-T, non-B-ALLs. (Author abstract) (32 Refs)

47. CIRCULATING IMMUNE COMPLEXES IN HUMAN ACUTE LEUKAEMIA.

Balestrieri G, Tincani A, Cattaneo R, Rossi G, Verzura P, Marini G, Calculli G, Ferremi P, Marinone G
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Br J Haematol; 49(2):269-274 1981

Circulating immune complexes (CIC) in the sera of 60 newly diagnosed leukemic patients were investigated by two methods, 125I-C1q binding test (C1q-BA) and conglutinin binding assay (KgB-SP). Positivity percentages were respectively 20.0% (C1q-BA) and 28.3% (KgB-SP). The small overlap between

the results of the two methods suggests the occurrence of different types of CIC. The presence of CIC was found to be related only to clinical hemorrhage and thrombocytopenia; it did not prove to affect the prognosis and the survival of leukemic patients. (Author abstract) (22 Refs)

48. T-LYMPHOCYTE SUBPOPULATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: A QUANTITATIVE AND FUNCTIONAL STUDY.

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Cancer; 48(10):2191-2197 1981

In the peripheral blood of patients with chronic B-cell lymphocytic leukemia (B-CLL) absolute numbers of E-rosetting lymphocytes were increased. The proportions of TG and TM cell subsets were analyzed, as were their effects on the pokeweed mitogen (PWM)-dependent differentiation of normal allogenic B cells of of autologous leukemic cells. The TG lymphocyte subset was further studied for its cytotoxic activity in antibody-dependent cellular cytotoxicity (ADCC). A marked increase both in percentages and in absolute numbers of TG cells was found. TM lymphocytes percentages were normal, but because of the T lymphocytosis occurring in all patients, the absolute numbers of TM were increased. TM and TG subsets showed helper and suppressor activity, respectively, in PWM-induced B-cell differentiation. TG cel ls displayed effector cell activity in ADCC. The results provide further evidence that T lymphocytes from patients with B-CLL are functionally normal. However, a noticeable increase of the T-cell subset having suppressor and cytotoxic activity in ADCC was observed. This may be the consequence of a normal immune reaction to the leukemic population. (Author abstract) (45 Refs)

49. THE USE OF BACTERIA AS MARKERS OF LEUKEMIC LYMPHOCYTES AND FOR THE ISOLATION OF NATURAL KILLER CELLS.

Teodorescu M, Hsu C, Bratescu A, DeBoer KP, Nelson R, Kleinman R, Wen CM, Mayer EP, Pang EJ
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Haematol Blood Transfus; 26:355-359 1981

A method was developed to separate various lymphocyte populations by bacterial adherence and functional difference. The mechanism of natural binding of bacteria to lymphocytes involves a lectin on the lymphocyte surface and a carbohydrate on the bacterium. Natural killer (NK) cells can be separated by negative selection using monolayers of bacteria. A subpopulation of T cells identified by binding to B globigii was shown to be suppressor for NK cells. Lymphocytes of 5/12 patients with acute lymphocytic leukemia were classified as pre-B cells based on a relatively low percentage of immunoglobulin positive (Ig+) cells but high percentage of lymphocytes binding Brucella melitensis (Bm), a B cell marker independent of surface Ig. Although the percentage of Ig-Bm+ cells was high in all five patients, the percentage of Ig+ cells was relatively low with a relatively normal chi/lambda ratio, suggesting that the cells were arrested at a stage of differentiation much earlier than that in which the surface Ig is exposed. Existence in one patient of a higher percentage of Ig+ cells than cells binding B melitensis suggests that the Ig may sometimes be exogenous. A patient with familial chronic myelocytic leukemia exhibited a relatively high percentage of Bm+ lymphocytes which was greater in peripheral blood than in bone marrow. Percentage of Ig+ cells was normal. This observation suggests that B cells and myelocytes may have an immediate common precursor. (13 Refs)

50. THE MIGRATORY PROPERTIES OF INDIUM-111 OXINE LABELLED LYMPHOCYTES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA.

Wagstaff J, Gibson C, Thatcher N, Crowther D
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Br J Haematol; 49(2):283-291 1981

These studies describe the application of a new method for following the migration of autologous lymphocytes in normal subjects and patients with chronic lymphocytic leukemia (CLL). There is evidence that Indium 111 oxine is a reliable radioactive cell label for in vivo studies of lymphocyte traffic in man. In normal subjects, where 60-70% of the lymphocytes labeled are T cells, the results are d ifferent from those of previous workers. The lymphocytes leave the blood initially but later return to it. It is believed that this is due to the reappearance of cells which at first entered the spleen. It is suggested that the difference between these data and those of Hersey (1971) is due to the failure of lymphocytes in the latter studies to return to the blood after primary migration. In CLL no such reappearance in the blood is seen and the lymphocytes do not leave the spleen in significant numbers over 48 hr. This suggests that CLL B cells either do not recirculate through spleen or that their transit time is greater than 48 hr. Bone marrow localization in CLL patients is greater than in the normal subjects, suggesting that either a larger proportion of the neoplastic B lymphocytes enter this compartment or their transit time through it is longer than the transit time of a normal T cell predominant population. Localization in normal-sized lymph nodes in patients with CLL is less than that in the lymph nodes of normal subjects. This may possibly be explained by the greater propensity of T lymphocytes to enter lymph nodes than B lymphocytes, or by the altered migratory properties of CLL B lymphocytes as compared with normal B cells. (Author abstract) (17 Refs)

51. BCG-VACCINATION, ITS INFLUENCE ON COURSE AND LETHALITY OF LEUKEMIA.

Ambrosch F, Wiedermann G, Krepler P, Kundi M, Ambrosch P
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Fortschr Med; 99(35):1389-1393 1981

As a retrospective study the clinical data of 613 leukemic children were collected. 269 of them were born in Austria, fell sick between 1967 and 1976 and were not older than 5 yr at the onset of disease. BCG-vaccination, which is performed in Austria within the first 3 days after birth, was checked by means of hospital reports, birth protocols and central BCG record. All data were stored and evaluated by electronic data processing. Besides a significant decrease of mortality, which we could demonstrate in earlier studies, the following correlations between BCG-vaccination of newborn and leukemia were found: Reduction of morbidity, decrease of case fatality, increase of 5 yr survival rate, increase of mean survival time, delayed onset of disease, decrease of frequency of myeloid and chronic leukemia. With the exception of the slight reduction of morbidity all correlations are significant. (Author abstract) (no Refs) (In GER)

52. A PHASE I STUDY OF HUMAN LYMPHOBLASTOID INTERFERON IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.

Rohatiner A, Balkwill F, Malpas JS, Lister TA
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Haematol Blood Transfus; 26:63-67 1981

Preliminary results of a Phase I study of human lymphoblastoid interferon (HLBI) in patients with acute myeloblastic leukemia (AML: 10), follicular non-Hodgkin's lymphoma (1), myeloma (1), and chronic lymphocytic leukemia (1) are described. All patients complained of general malaise and anorexia, and became pyrexial between 2 and 24 hr after administration of HLBI. Of the 13 patients, 4 complained of rigors, 3 of headaches, and 1 of joint pains. One patient experienced a hypotensive episode after the second injection of HLBI. All patients had bone marrow infiltration rendering interpretation of the blood count extremely difficult. In patients with AML, a fall in Hb and platelet counts was compatible with advancing disease. No evidence of renal impairment was found; liver function tests remained normal. Serum interferon activity was measured. The results indicated that up to 10 x 10(6) unit/square meter iv can be given daily; to avoid toxicity and achieve consistent levels, iv HLBI should be given by continuous infusion. After iv injection of HLBI, high peak levels were achieved at 30 min, but interferon was rapidly cleared in the first hr after injection. When given by continuous iv infusion, interferon levels increased over 72 hr and then remained elevated. Results of the in vitro study confirmed the cell growth inhibitory effects of HLBI on human myeloblasts. The degree of growth inhibition was dose dependent. However, the concentration of interferon that resulted in 50% inhibition of growth in vitro was 3-10x higher than the serum levels attained. (7 Refs)

CHEMOTHERAPY

53. INDUCTION AND CONSOLIDATION COMBINATION CHEMOTHERAPY WITH 8 DRUGS (L-10 PROTOCOL) FOR ACUTE LYMPHOBLASTIC LEUKEMIA.

Carella AM, Nicolino M, Santini G, Occhini D, Damasio EE, Rossi E, Giordano D, Vimercati R, Risso M, Bacigalupo A, Carubia F, Spriano M, Van Lint MT, Taroppio T, Pittaluga A, Marmont AM
vico S. Barborino, 7/82, Genova Sampierdarena, Italy
Haematologica (Pavia); 66(3):311-326 1981

Results obtained with chemotherapy for adult acute lymphoblastic leukemia (ALL) using the Sloan Kettering L-10 protocol are reported. Three-phase therapy was administered to 16 patients (av age 22 yr, 75% male): induction [vincristine (VCR), methylprednisolone (MP), adriamycin], consolidation [methotrexate (MTX), cytarabine, thioguanine, L-asparaginase, cyclophosphamide], and maintenance (reinduction with VCR and MP, MTX, 6-mercaptopurine, dactinomycin, cyclophosphamide, and carmustine). All patients received intrathecal MTX (6 mg/square meter) and cytarabine (15 mg/square meter) for CNS prophylaxis. Of 16 patients 15 were high risk. By cytologic classification one patient was L1, 9 L2, and 6 L3. Immunologically 13 patients were null-ALL and 3 were T-ALL. Of 16 patients 14 (87.7%) had complete hematological remission, which lasted av 7.9 mo; survival time was av 16 mo. Eight patients relapsed within 7 mo, and one after 25 mo. Presently 7 patients are living: 3 in first remission and 4 in third remission. For second and third remissions different protocols were tried. Authors do not consider chemotherapy useful in advanced cases; bone marrow transplant administered during remission offers the only possible hope for adult ALL. (38 Refs) (In ITA)

54. VAPA: A TREATMENT PROGRAM FOR ACUTE MYELOCYTIC LEUKEMIA.

Mayer RJ, Weinstein HJ, Rosenthal DS, Coral FS, Nathan DG, Frei E
Sidney Farber Cancer Inst., 44, Binney St., Boston, MA, 02115
Haematol Blood Transfus; 26:45-52 1981

The status of the VAPA protocol (remission induction with adriamycin, (ADR) cytosine arabinoside (Ara C), vincristine (VCR) and prednisolone, and maintenance therapy with an intensive sequential combination of ADR, Ara C, azacytidine, 6-mercaptopurine, VCR, methotrexate, and methylprednisolone), as used to treat 106 consecutive, previously untreated patients less than 50 yr old with acute myelocytic leukemia, is described. At the time of April 1, 1980 review, 105 patients were evaluable for analysis, with 61 being 17 yr old or younger and 44 being 18-50 yr old. Complete remission were obtained in 74/105 patients, with younger patients having a slightly increased chance of achieving a complete remission (74%) than their older counterparts (66%). Among the 74 complete responders, there were 8 withdrawals. Of these eight patients, seven remained in their initial complete remission. Two remission deaths were reported. Among the remaining 64 patients who entered complete remission, 40 remained disease-free, while 24 relapsed. All relapses in the adult age group occurred in bone marrow. In contrast, 1/2 of the 16 pediatric age relapses occurred in the CNS. Of the 22 patients who completed the VAPA program, 4 relapsed 'off therapy', and 18 remained in unmaintained complete remission. The median survival for the entire group of 105 patients was 26.1 mo. The major toxicity of the VAPA program was fever. The results indicated that AML can be suppressed for extended periods of time by chemotherapy alone in at least 33% of patients under age 50. (26 Refs)

55. INTENSIVE THERAPY AND PROGNOSTIC FACTORS IN ACUTE LYMPHOBLASTIC LEUKEMIA OF CHILDHOOD: CCG 141.

Miller DR, Leiken S, Albo V, Sather H, Karon M, Hammond D
Childrens Cancer Study Group, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Haematol Blood Transfus; 26:77-86 1981

Results of treatment regimens for childhood acute lymphoblastic leukemia (ALL) are presented; prognostic groups are redefined based on prospective evaluation of front-end factors. Patients were assigned to treatment (low: LR1 or high: HR1 or R2) based on WBC counts. Drugs administered and dosage schedules are presented. Of the 882 eligible patients, 576 were entered on LR1, 151 on HR1, an d 155 on R2; complete remission rates were 95%, 93%, and 91%, respectively. Significantly unfavorable factors of response to induction therapy were age greater than 10 yr, initial WBC greater than 20 x 10(9)/liter, presence of CNS disease at diagnosis, L2 or L3 morphology, decreased IgG, Down's syndrome, and less than 30% PAS positive lymphoblasts. Marrow status on day 14 of induction was also a significant predictor: 454/455 of children with M1 marrow on day 14 were M1 at completion of induction and 57/70 with M3 marrow on day 14 were M1 on day 28 or 42 of induction. Duration of complete continuous remission (CCR) and hematologic remission were longer and relapse rate lower

in children entered on LR1 than in patients entered on HR1 and R2. At 48 mo, 65.2%, 48.1%, and 39.1% of patients on LR1, HR1, and R2, respectively, remained in CCR. Of the patients completing induction, 57.6% remained in CCR. No significant differences in relative relapse rates were observed in the regimens. The incidence of isolated CNS relapse in LR1, HR1, and R2 was 4.7%, 8.5%, and 12.8%, respectively. During maintenance therapy, testicular relapse occurred in 44 of 459 boys at risk. The testicular relapse was significantly higher in HR1 than in R2 or LR1. Isolated bone marrow, CNS, and testicular relapses occurred in 204, 57, and 34 patients, respectively. Prognostic factors for disease-free survival and survival are presented. (19 Refs)

56. PROGRESS IN ACUTE MYELOGENOUS LEUKEMIA.

Lister TA, Johnson SA, Bell R, Henry G, Malpas JS
Dept. Medical Oncology, St. Batholomew's Hosp., West Smithfield, London EC1A 7BE, England
Haematol Blood Transfus; 26:38-44 1981

Selected data from studies in which 588 consecutive adults with acute myelogenous leukemia (AML) were treated, 443 (243 men, 200 women; 14-77 yr old) of them with combination chemotherapy in prospective trials, are presented. Exclusions from the trials were made because of advanced age and extensive prior chemotherapy. Complete remission was achieved in 187/443 patients. The two most important factors correlating with the response to therapy were age of patient at presentation and the initial treatment received. The complete remission rate was significantly higher for patients under the age of 60 yr. It was also significantly higher for patients receiving intensive chemotherapy comprising adriamycin, cytosine arabinoside, and 6-thioguanine, especially for the group under 60 yr old. Thrombocytopenia upon presentation was a poor prognostic factor overall, with complete remission only being achieved in 29/96 patients in whom the platelet count was less than 20 x 10(9)/liter compared with 158/347 in whom it was more. Of 187 patients in whom complete remission was achieved, 50 remained alive without relapse and three died in complete remission. Possible factors influencing the duration of the first complete remission, including the intensity of the initial therapy and continuation of therapy, are discussed. The most important factor determining survival was the outcome of initial therapy. Thirty-six patients have lived more than 3 yr. The results confirmed the trend reported by others that intensification of early therapy can result in complete remission being achieved in the majority of adults under the age of 60 yr. (12 Refs)

57. RATIONAL APPROACHES TO THE TREATMENT OF LEUKEMIA.

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Haematol Blood Transfus; 26:53-58 1981

Treatment of acute myelocytic leukemia (AML) patients (less than 70 yr old) after achievement of remission with intensive chemotherapy to reduce and/or ablate any remaining leukemia cells is reported. Factors which determine response to therapy are considered. Comparison of remission duration of patients treated with different chemotherapy regimens suggested that the more intensive post-remission induction treatment resulted in a reduction in number of early relapses and longer median duration of remission with a higher proportion of patients in remission beyond yr 2. Early intensive consolidation chemotherapy may prolong remission duration by reducing the number of leukemic cells remaining after remission induction therapy is administered. The outcome of remission induction therapy was determined by both the patient's ability to survive remission induction therapy and by the drug sensitivity of a patient's leukemic cells. The method used to determine sensitivity of leukemic cells to cytarabine and daunorubicin and the relationship between in vitro sensitivity and outcome of remission induction therapy with the two agents are described. A clear-cut relationship between percentage of clonogenic leukemic cells killed by the two drugs and in vivo response to therapy was observed. (14 Refs)

58. IMPROVED SURVIVAL FROM ACUTE LYMPHOBLASTIC LEUKEMIA IN ADOLESCENTS AND ADULTS.

Blacklock HA, Matthews JR, Buchanan JG, Ockelford PA, Hill RS
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Cancer; 48(9):1931-1935 1981

Nineteen adult patients with acute lymphoblastic leukemia were treated with combination chemotherapy to induce remission in the period from 1971 to 1979. Those patients achieving remission received intensive post-remission therapy with CNS prophylaxis, followed by two-drug maintenance therapy, and reinduction courses of chemotherapy every 6 mo. Remissions were achieved in 17 of the 19 patients (89%). Twelve patients (63%) are alive, 11 currently in complete remission. Two patients who experienced relapses in recent mo have successfully undergone transplantation with allogeneic marrow from sex-matched, HLA-compatible sibling donors. The median survival and median duration rates of first remissions have not yet been reached, but to date are 36+ mo and 29+ mo, respectively with a predicted 5-yr survival rate of 61%. These results not only are significantly better than those achieved in the yr 1968 to 1971 in our institution, but also are superior to others reported in the world medical literature. The combination of optimal treatment protocols with allogeneic marrow transplantation for patients with poor prognoses is expected to improve the survival of adult patients even further in the next decade. (Author abstract) (29 Refs)

59. A TRIAL OF VINCRISTINE THERAPY IN CHRONIC PHASE OF CHRONIC MYELOCYTIC LEUKEMIA.

Kamada N, Okada K, Saito O, Oguma N, Tanaka K, Dohy H, Kuramoto A, Sawada H, Uchino H
Internal Medicine, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan
Nippon Ketsueki Gakkai Zasshi; 44(5):1050-1053 1981

To assess the effectiveness of vincristine as a supplementary therapy to busulfan-treatment in Ph1 positive chronic myelocytic leukemia on the onset of the blastic crisis of the disease and on the overall survival time, 'Intermittent Vincristine Therapy' was performed on 16 cases in chronic phase of the disease. One mg of vincristine was injected iv once a wk for 4 wk, while the minimum dose of busulfan for maintaining proper WBC count was administered. The patients underwent the same course at 6 or 9 mo intervals. WBC counts, RBC counts, Hb and platelet counts, differential counts of WBC and neutrophil alkaline phosphatase scores were examined prior to, and after 2 or 3 wk of the injections. After the treatment, no remarkable changes were observed in the peripheral blood. Side effects were observed on two occasions during the 34 courses of the treatment, one severe constipation and the other hypergeusia. Both, however, recovered or improved within a few days. Six out of the 16 treated cases transformed to blastic crisis without any lymphoblastic conversion. 'Intermittent Vincristine Therapy' reported here seems to be a possible therapy for patients

with chronic myelocytic leukemia in chronic phase without any severe side effects. (Author abstract) (12 Refs) (In JPN)

60. CARDIOTOXIC ASPECTS IN THE TREATMENT OF ACUTE MYELOBLASTIC AND LYMPHOBLASTIC LEUKEMIAS WITH DAUNORUBICIN.

Topalov V, Popovic K, Cikos J, Pejin D, Uzurov V
Medicinski fakultet, Novi Sad, Yugoslavia
Med Pregl; 34(3/4):119-122 1981

The cardiotoxicity of daunorubicin (DNR) was studied in 33 patients with leukemia (18 men, 15 women, av age 45.5 yr). Acute myeloblastic leukemia was diagnosed in 29 cases and acute lymphoblastic leukemia in 4. Thirteen patients were treated with Daunoblastin and 20 with Adriblastin. The electrocardiographic (ECG) examinations performed before therapy showed sinus tachycardia (ST) in 7 cases, absolute arrythmia (AA) in 1, and changes of the T waves and ST segment in 3. The ECG recorded after treatment showed ST in 15 cases, supraventricular paroxysmal tachycardia in 4, AA in 3, supraventricular extrasystole in 1, ventricular extrasystole in 2, ventricular fibrillation in 1, and changes of the T waves and ST segment in 11. Toxic myocarditis was found in two patients after administration of total doses of 315 and 420 mg, respectively. The changes were more frequent in patients treated with Daunoblastin than in those treated with Adriblastin. Slightly lowered systolic pressure, elevated diastolic pressure, normalization (fall) of body temperature and heart rate, and a rise in the erythrocyte count were found after administration of several doses of DNR. (20 Refs) (In SCR)

61. USE OF VM-26 (EPIIODOPHILOTOXIN) IN THE TREATMENT OF ACUTE LEUKEMIAS AND LYMPHOMAS IN ADULTS.

Kondrat'eva NA, Gershanovich ML, Kondrat'ev VB, Lebedev VN, Vygovskaia Ial, Iavorkovskii LI
Dept. Cooperative Studies in Clinical Oncology, Cancer Res. Center, Moscow, USSR
Probl Gematol Pereliv Krovi; 26(7):10-14 1981

The results of the cooperative clinical trials of VM-26 (epiiodophilotoxin) in 80 patients (40 men, 40 women, 15-70 yr old) Hodgkin's disease (HD), lymphosarcoma (LS), and acute leukemia (AL) are reported. Of 80 patients, 53 received short, 5-day, courses of VM-26 (30 mg/square meter, iv) with 10-day intervals between the courses, and 27 received long courses (40 mg/square meter, iv, 2x/wk, for 3-4 wk). Complete and partial remissions were recorded in 18.6% and 7.5% of the patients with HD, 21.4% and 35.8% of the patients with LS, and in 2.6% and 10.2% of the patients with AL. Subjective improvement was achieved in 33.3% of the patients with HD, 21.4% of the patients with LS, and in 12.8% of the patients with AL. Side-effects were nausea and vomiting (55.5% in HD, 42.8% in LS, and 12.8% in AL), marked fatigue (18.5%, 7.1%, and 5.1%, respectively), and leukopenia (44.4%, 21.4%, and 25.6%, respectively). (11 Refs) (In RUS)

62. TREATMENT OF EARLY ACUTE NONLYMPHATIC LEUKEMIA WITH LOW DOSE CYTOSINE ARABINOSIDE.

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Haematol Blood Transfus; 26:59-62 1981

Two patients (78-yr-old man, 43-yr-old woman) with early acute nonlymphatic leukemia (ANLL) and seven patients with RDA-ANLL were treated with low-dose cytosine arabinoside (Ara-C). Observations on these cases and preliminary findings on the effect of low-dose Ara-C on leukemic cells cultured in diffusion chambers are presented. Remissions were obtained in both ANLL patients. Three sideroblastic RDA-ANLL cases failed to respond to several courses of low-dose Ara-C. It was too early to evaluate results of low-dose Ara-C therapy in the other 4 RDA-ANLL patients. Observations of the effect of low-dose Ara-C on growth and maturation of marrow cells were carried out by treating host rats with 0.1 mg/kg Ara-C daily, sc for 21 days. The pretreatment marrow cells of one ANLL patient showed a striking neutrophilocytosis on day 5 followed by an intense lymphocytosis from days 8-14. In the untreated control cultures, a similar but less intense cellular response occurred. In four cases of RDA-ANLL and one nonleukemic RDA, an effect on maturation by low dose Ara-C was noted in two instances but was equivocal in three other patients. In one case of de novo ANLL myeloblasts proliferated actively and neither growth nor maturation was influenced by Ara-C. (6 Refs)

63. TREATMENT OF ACUTE NONLYMPHOCYTIC LEUKEMIA IN ADULTS: RESPONSE TO 2,2-ANHYDRO-1-B-D-ARABINOFURANOSYL-5-FLUOROCYTOSINE AND THIOGUANINE ON THE L-12 PROTOCOL.

Mertelsmann R, Drapkin RL, Gee TS, Kempin S, Passe S, Thaler HT, Arlin Z, Dowling M, Dufour P, McKenzie S, To L, Comacho E, Oettgen HF, Burchenal JH, Clarkson B
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 48(10):2136-2142 1981

Fifty-one adult patients with acute nonlymphocytic leukemia (excluding acute promyelocytic leukemia) were treated on the L-12 protocol. The L-12 differed from the preceding L-6 in that 2,2-anhydro-1-B-D-arabinofuranosyl-5-fluorocytosine (AAFC), replaced arabinosylcytosine (ara-C) together with 6-thioguanine (TG) for remission induction. Achievement of remission was followed by an extended 14-wk multi-drug consolidation program. With this more intense regimen, an overall complete remission rate of 49% and a median remission duration of 23.7 mo were achieved; these results were not significantly better than the 57% complete remission rate and 8.6 mo median remission duration obtained with the L-6 regimen. Four yr disease-free survival was 22% on the L-12 compared with 16% on the L-6 protocol. No relationship between prognosis and FAB classification was found on either the L-6 or the L-12 protocol. (Author abstract) (26 Refs)

64. THE EFFECTS OF ANTI-LEUKEMIC THERAPY ON GONADAL HISTOLOGY IN ADULT MALES.

Maguire LC, Dick FR, Sherman BM
Lexington Clinic, 1221 South Broadway, Lexington, KY, 40504
Cancer; 48(9):1967-1971 1981

Testicular histologic findings in 29 male patients who died of acute leukemia or blastic phase of chronic myelogenous leukemia are reviewed to evaluate the effect of therapy on morphology. Four histologic groups were identified that correlated with the duration of treatment: (1) normal testes associated with no therapy or therapy for less than 30 days; (2) maturation arrest in those treated for 5 days to 40 mo; (3) hypospermatogenesis in those treated from 17 days to 84 mo; and (4) Sertoli cells only in those treated from between 3 and 63 mo. These histologic patterns correlated more with the duration of therapy than the type of anti-leukemic therapy used.

There was some variability in the histologic effects among individuals receiving comparable durations and types of chemotherapy. In many patients who received extensive therapy, spermatogonia remain which may allow recovery of spermatogenesis and fertility. (Author abstract) (21 Refs)

65. LEVELS OF 2'-DEOXYCOFORMYCIN, ADENOSINE, AND DEOXYADENOSINE IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Venner PM, Glazer RI, Blatt J, Sallan S, Rivera G, Holcenberg JS, Lipton J, Murphy SB, Poplack DG
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Cancer Res; 41(11,part1):4508-4511 1981

A potent inhibitor of adenosine deaminase, 2'-deoxycoformycin (dCF), has recently undergone Phase I clinical trials and has been found to be therapeutically active in acute lymphoblastic leukemia. In this report, levels of dCF in plasma, plasma concentrations of adenosine and deoxyadenosine, and urine levels of deoxyadenosine were measured in leukemic patients undergoing treatment with dCF during a Phase I clinical trial. dCF was administered iv at a dose of 0.25 to 1.0 mg/kg (7.5 to 30 mg/sq m) for 3 consecutive days. Plasma drug levels of 2 to 6 uM were observed following the third dose of dCF, and drug accumulation occurred only at the 1-mg/kg dosage. In this limited series of patients, the plasma concentrations of adenosine and deoxyadenosine and the urine concentration of deoxyadenosine did not show an obvious correlation with dCF dose, therapeutic response, or toxicity. (Author abstract) (21 Refs)

66. L-ASPARAGINASE PHARMACOKINETICS AND ASPARAGINE LEVELS IN CEREBROSPINAL FLUID OF RHESUS MONKEYS AND HUMANS.

Riccardi R, Holcenberg JS, Glaubiger DL, Wood JH, Poplack DG (c/o Poplack) Pediatric Oncology Branch, NCI, Building 10, Room 3B-03, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4554-4558 1981

L-Asparaginase has been widely used for the treatment of acute lymphoblastic leukemia. Therapeutic and toxic effects in the CNS have been noted with systemic treatment. In order to better define the relationship between L-asparaginase administration and cerebrospinal fluid (CSF) asparagine levels, L-asparaginase and asparagine were measured in the CSF of rhesus monkeys following intrathecal and iv administration. Following intrathecal injection, the enzyme activity of Escherichia coli L-asparaginase in the CSF demonstrated a more rapid terminal half-life than did that of 111In-labeled diethylenetriaminepentaacetic acid, a marker of CSF bulk flow [4 +-0.7 (SD) hr vs 5.8 +-0.2 hr]. Intrathecal injection of L-asparaginase resulted in complete depletion of CSF asparagine for at least 5 days. A similar period of CSF asparag ine depletion was observed following iv administration of E coli L-asparaginase. Similar results were found in seven patients undergoing systemic L-asparaginase therapy. The minimal plasma level of L-asparaginase necessary to deplete CSF asparagine in both species was 0.1 IU/ml. Two other enzymes, Erwinia L-asparaginase and succinylated Acinetobacter glutaminase-asparaginase, were cleared from the CSF at the same rate as bulk flow. These data indicate that systemic L-asparaginase therapy may be a feasible means of treating CNS involvement in patients with acute lymphoblastic leukemia and that there is no therapeutic advantage to using intrathecal L-asparaginase. (Author abstract) (28 Refs)

67. RECURRENT CHILDHOOD LYMPHOCYTIC LEUKEMIA: OUTCOME OF MARROW RELAPSES AFTER CESSATION OF THERAPY.

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Haematol Blood Transfus; 26:94-98 1981

Clinical course of 56 patients retreated for bone marrow relapses that developed after cessation of intensive initial treatment is reviewed. Of 288 children in whom treatment for acute lymphocytic leukemia was stopped after 2-3 yr of complete remission, 72 relapsed, 56 with bone marrow recurrences. In 43/56 only marrow was involved, but in the remaining 13 testes and CNS were involved as well. Seventeen children with leukemia in relapse received reinduction chemotherapy with prednisone, vincristine and adriamycin (4 wk), and all were randomized at the time of remission to receive or not receive an intensive phase of chemotherapy with asparaginase and cytosine arabinoside (Ara-C). Continuation therapy consisted of mercaptopurine and methotrexate (MTX). CNS prophylaxis was not used. Sixteen patients attained second remission, with a median duration of 10 mo. Each child relapsed again, eight in the marrow and six in the CNS. In 4/7 patients, remissions were again induced; 3/4 children relapsed after 1-7 mo, but 1/4 remained in remission 48+ mo after the end of treatment. In view of the rate of relapse and moderate toxicity encountered, another 23 patients received the same reinduction therapy with the addition of four weekly injections of MTX and Ara-C, 30 mo of continuation therapy with Ara-C and MTX along with intrathecal injections every 6 wk, a late intensive phase of chemotherapy with vincristine, prednisone, and adriamycin, and CNS prophylaxis. All 23 patients attained complete remission. The median duration of hematologic remission was 14 mo (3-50+). Although 14 patients relapsed in the marrow, none developed CNS relapse. The results indicated that prolonged second remissions are attainable in approx 1/3 of patients who develop marrow relapse after elective cessation of cure-oriented therapy. (14 Refs)

68. ABSENCE OF ISOLATED TESTICULAR RELAPSE (ITR) IN CHILDHOOD ACUTE LYMPHOBLASTIC LE UKEMIA (ALL) WITH A REPETITIVE REINDUCTION PROTOCOL (MEETING ABSTRACT).

Ravindranath Y, Warrier R
No affiliation given
J Pediatr; 98(6):1022 1981

Our data are in sharp contrast to the published reports of ITR. We have not encountered ITR as the sole initial relapse in any of 101 boys with ALL treated at our institution over an 11-yr period. Ten patients had mediastinal mass at presentation and 41 had WBC 20,000/mm3 at diagnosis. All were treated (for 5 yr) with identical chemotherapy and the last 62 patients in addition received intermittent intrathecal methotrexate (MTX) and fractional irradiation (IMFRA) CNS prophylaxis. Remission was induced with vincristine (VCR) 2 mg/m2, plus 6-mercaptopurine (6-MP) 2 mg/kg, and prednisone (Pred) 60 mg/m2 and maintained with alternating cycles of biweekly oral MTX 30 mg/m2 for 6 wk, and VCR + 6-MP + Pred for 4 wk. IMFRA CNS prophylaxis is given every 10 wk. The median duration of complete remission was 18 mo (range 1-20 mo) for patients prior to the introduction of CNS prophylaxis and it has not yet been reached in those receiving CNS prophylaxis (range 1-95 mo). Five of 26 patients off therapy had relapse (3 bone marrow (BM), 1 CNS, and 1 simultaneous BM and CNS). Thus in a group of boys with ALL treated with a

repetitive reinduction protocol, as described above. ITR as the sole initial recurrence was not seen on or off therapy. This suggests that an effective maintenance program prevents ITR and that the testis may not be a sanctuary site. (no Refs)

69. THE TREATMENT OF PRIMARY CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA WITH INTERMEDIATE DOSE METHOTREXATE.

Sinks LF, Wang JJ, Freeman AI
No affiliation given
Haematol Blood Transfus; 26:99-107 1981

Fifty-four patients with newly diagnosed acute lymphocytic leukemia received treatment including systemic intermediate dose methotrexate (IDM: 500 mg/square meter) given over 24 hr in an attempt to eradicate leukemia cells in the CNS. Of the 54 patients, 52 achieved complete remission. During a follow-up of 36-72 mo, 20 patients experienced relapse: 10 CNS, 9 systemic, and 1 testicular. Eleven of the 17 increased-risk patients and 9/35 standard-risk patients relapsed. In the nine standard-risk patients who relapsed, five recurrences were CNS, three systemic, and one testicular. Of the 11 increased-risk patients who relapsed, 5 were in the CNS and 6 were systemic. Of the 52 children who entered complete remission, 8 died. IDM toxicity included vomiting (20/52), oral ulceration (20/52), hematologic toxicity (12/52), hepatic toxicity (11/52), and transient maculopapular rashes (3/52). The overall regimen was well-tolerated. Results indicated that the use of a systemic as opposed to local [radiotherapy (RT) to the cranium] form of therapy confers greater protection on standard-risk children with ALL. The long-range complication of cr anial RT can also be avoided. In high-risk patients, cranial RT and intrathecal methotrexate appears superior to IDM. (32 Refs)

RADIOTHERAPY

70. EVALUATION OF RADIATION THERAPY FACTORS IN PROPHYLACTIC CENTRAL NERVOUS SYSTEM IRRADIATION FOR CHILDHOOD LEUKEMIA: A REPORT FROM THE CHILDREN'S CANCER STUDY GROUP.

D'Angio GJ, Littman P, Nesbit M, Sather H, Hittle R, Ortega J, Donaldson M, Hammond, D
Children's Cancer Study Group Operations Offace, 1721 Griffin Ave., Los Angeles, CA, 90031
Int J Radiat Oncol Biol Phys; 7(8):1031-1038 1981

The toxicity, survival experience, CNS and bone marrow relapse rates for 656 leukemia children are reported in relation to such radiation therapy factors as the fields employed, doses administered, and the different technical approaches used. Study design called for remission induction using vincristine, prednisone, and L-asparaginase. Patient achieving M1 bone marrow status 28-42 days after initiation of treatment were eligible for randomization among four treatment groups, as follows: (1) cranio-spinal radiation therapy (RT) to 2,400 rad plus 1,200 rad to thymus, abdomen, testes;(2) cranio-spinal RT (2,400 rad); (3) cranial RT (2,400 rad) plus intrathecal methotrexate (IT/MTX: 12 mg/square meter, twice weekly for 3 wk); (4) IT/MTX alone as in regimen 3; (5) craniospinal radiation at 1,800 rad; (6) cranial RT at 1,800 rad plus IT/MTX. No statistically significant differences could be detected in the CNS, bone marrow relapse, relapse-free survival or survival rates among the five irradiated groups. There were no consistent differences in these results when equipment factors, daily dose, total dose, duration of treatment, or field arrangements were analyzed. Group 1, 2, and 5 patients, who had larger fields irradiated, encountered more complications. (15 Refs)

71. HYPERFRACTIONATED TOTAL BODY IRRADIATION OR BONE MARROW TRANSPLANTATION: I. EARLY RESULTS IN LEUKEMIA PATIENTS.

Shank B, Hopfan S, Kim JH, Chu FC, Grossbard E, Kapoor L, Reid A, Chui C, Mohan R, Finegan D, O'Reilly RJ
Radiation Therapy Dept., Memorial Sloan-Kettering Cancer Cener, New York, NY, 10021
Int J Radiat Oncol Biol Phys; 7(8):1109-1115 1981

A hyperfractionated total body irradiation (TBI) regimen, with partial lung blocking, was developed to reduce the incidence of radiation interstitial pneumonitis (IP) in leukemia patients undergoing bone marrow transplantation. Hyperfractionated TBI (120 rads x 11; 3 x/day) decreased both IP incidence and deaths attributable to IP in 48 patients (mean age, 18 yr; range, 1.5-42 yr) with acute nonlymphocytic leukemia (ANLL), acute lymphocytic leukemia (ALL), and chronic myelocytic leukemia Sixteen patients (33%) developed IP, compared with 14/20 (70%) patients treated earlier with single dose irradiation (1,000 rads). The percentage of deaths related to IP decreased from 50% (10/10) in the earlier series to to 23% (11/48) with fractionated TBI. The 1-yr actuarial survival was 65% for ALL (16 patients) and 72% for ANLL (29 patients). Patients who died and patients who developed IP had a mean age of 25 yr. (11 Refs)

OTHER THERAPEUTIC MODALITIES

72. GLUCOCORTICOID RECEPTORS IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA.

Bloomfield CD, Smith KA, Peterson BA, Munck A
Univ. Minnesota Hosp., Box 277, Mayo Building, Minneapolis, MN, 55455
Cancer Res; 41(11,part2):4857-4860 1981

Glucocorticoid receptors were studied in leukemic cells from 14 newly diagnosed adults with acute lymphoblastic leukemia. Receptors were found in all cases; total receptor levels ranged from 1,348 to 18,697 sites per cell (median, 7,553). To determine the utility of glucocorticoid receptor levels for predicting response to glucocorticoid therapy, lymphoblasts were studied for receptors on nine occasions, and the patients were then treated with dexamethasone as a single agent. Response to glucocorticoid therapy appeared to correlate with lymphoblast receptor level. Five of six patients with greater than 4,500 total receptor sites per cell responded; all three patients with less than 4,500 receptors failed to respond. Glucocorticoid receptor level did not correlate with response to combination chemotherapy, duration of remission, or survival. Glucocorticoid receptors were studied at the initial presentation and following relapse in five patients. In two patients, the receptor level did not change following therapy; both patients at diagnosis had leukemias resistant to glucocorticoids. Three patients at relapse developed leukemias with lower receptor levels; these patients had leukemias sensitive to glucocorticoids at diagnosis. Our data suggest that the glucocorticoid receptor levels of lymphoblasts may be useful in predicting response to glucocorticoid therapy in adult acute lymphoblastic leukemia. They also

suggest that, following relapse, cases initially sensitive to glucocorticoid may develop resistance by selection of cells with fewer receptors. (Author abstract) (17 Refs)

MULTIMODAL THERAPY

73. T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN.

Sallan SE
Sidney Farber Cancer Inst., 44, Binney St., Boston, MA, 02115
Haematol Blood Transfus; 26:121-123 1981

A new treatment program including chemotherapeutic agents more selective for T-cells (cyclophosphamide, cytosine arabinoside, adriamycin) along with vincristine and prednisone, intensification of the therapy to extramedullary sites, and thymectomy was used to treat 17 patients with immunologically proven T-cell acute lymphoblastic leukemia. Two patients died of sepsis and pneumonitis during induction. Of the 15 patients who entered complete remission, 3 relapsed at 5, 12, and 12 mo. Relapses were in the bone marrow (2) and CNS (1), respectively. Three remission deaths occurred at 3, 8, and 12 mo, two from sepsis and one from adriamycin-induced cardiomyopathy. Eleven patients remained in continuous remission from 7+ to 28+ mo. Median follow-up was 15 mo. Two patients elected to discontinue therapy and remained disease-free for 28 mo. (9 Refs)

74. COMBINATION OF CHEMOTHERAPY, RADIOTHERAPY AND IMMUNOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN.

Suvatte V, Mahasandana C, Tanphaichitr VS, Tuchinda S, Vootiprux V
Dept. Pediatrics, Siriraj Hosp., Mahidol Univ., Bangkok 7, Thailand
J Med Assoc Thai; 64(4):180-191 1981

From 1967 to 1979, 51 children (4 mo to 12 yr old; 30 boys, 21 girls) with acute lymphoblastic leukemia (ALL) were treated with a combination of chemotherapy, radiotherapy and immunotherapy. The plan of treatment depended on the economic status of the family. Two different protocols were used, differing in their use of vincristine and L-asparaginase (used in Protocol I and not in Protocol II) because of their expense. Twenty-six patients received Protocol I and 25, Protocol II. Fifteen patients (57.7%) in Protocol I and 13 (53%) in Protocol II were in continuous hematological remission from 22 mo to 13 yr. Eleven patients in each protocol died. Treatment was discontinued at 5 yr in 10 patients, nine of whom were still in complete remission and in good health from 5.5-13 yr after diagnosis. Since complications and toxicity in patients treated with Protocol I were similar to those seen in Protocol II and the results of treatment in both protocols were similar, the use of combined simple, non-expensive drugs was shown to be as effective as the use of expensive drugs. (44 Refs)

SUPPORTIVE CARE

75. BONE MARROW TRANSPLANTATION FOR THE TREATMENT OF LEUKEMIA.

Storb R
Div. Oncology, Providence Hosp., 500 17th Ave, Seattle, WA, 98122
Haematol Blood Transfus; 26:136-138 1981

Patients with acute nonlymphoblastic leukemia (ANLL) were treated by bone marrow grafting in first or subsequent remission and those with acute lymphoblastic leukemia (ALL) in second or subsequent remission were treated using the basic conditioning regimen of cyclophosphamide and total body irradiation. Of the 19 ANLL patients, 12 were alive in continued unmaintained remission with a functioning marrow graft between 27 and 48 mo after transplantation. Of the 12, 9 were entirely well and 3 had mild chronic graft-vs-host (GVH) disease. Six of the 19 ANLL patients died from GVH disease and/or interstitial pneumonia. Only 1/19 of the patients had a recurrence of leukemia. Of the 22 ALL patients grafted, 3 died on interstitial pneumonia within 3 mo of grafting and 11 died of recurrent leukemia within 27 mo. The median survival of this group of transplanted patients was 1 yr. Of the 22 ALL patients, eight were surviving at 32-41 mo after transplantation in unmaintained remission. Seven of the eight patients were without problems and one had moderately severe chronic GVH disease. Four patients with chronic myelogenous leukemia (CML) were treated with a combination of total body irradiation, dimethylbusulfan, and cyclophosphamide followed by marrow infusion. Complete hematologic and cytogenetic remission was induced in all four. One patient relapsed at 30 mo, while the other three were clinically, hematologically, and cytogenetically normal at 36, 39, and 44 mo. (11 Refs)

76. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN FIRST REMISSION.

Morgenstern GR, Powles RL
No affiliation given
Haematol Blood Transfus; 26:139-142 1981

The place of bone marrow transplantation (BMT) in the treatment of acute myeloid leukemia (AML) is defined. Two groups of first remission patients treated either with BMT or chemoimmunotherapy are described. Thirty-three AML patients received a BMT, 27 from human leukocyte-A-identical and MLC-compatible sibling donors, two from identical twin donors, and four from related mis-matched donors. The outcome of the matched allografted patients was compared with the simultaneous group of 33 AML patients who did not receive a transplant and were maintained on chemo- and immunotherapy. Of the 33 patients treated with chemoimmunotherapy, 20 relapsed with a median remission duration of 12 mo compared with four of the matched allografted patients (p less than 0.001). Twelve of the 33 chemoimmunotherapy patients died (11 of relapse and 1 of infection while in remission) with a median survival of 21 mo from date of complete remission. There were five deaths in the matched allografted patients, 1 of relapse, and 4 of graft-vs-host disease, with or without pneumonitis. Actuarial analysis revealed that at no time did the transplanted patients fare worse and that they have a 75% 3-yr actuarial survival compared with 45% for the chemoimmunotherapy patients. Nineteen matched allografted patients remain alive in continuous remission compared with 12 in the chemoimmunotherapy group (p less than 0.01). (5 Refs)

77. INFECTION IN CHILDREN WITH ACUTE LEUKEMIA.

Carrillo JM, Jimenez F E, Jimenez B R
Catedra de Pediatria, Facultad de Medicina, Universidad de Costa Rica, San Jose, Costa Rica
Bol Med Hosp Infant Mex; 38(2):313-322 1981

Of 82 children studied, 72 had acute lymphocytic leukemia and 10 acute nonlymphocytic leukemia; 43 were female and 39 male, aged 4 mo to 15 yr, av 5 yr 8 mo. Children came from rural (44) and urban areas (38). Origin of 125 febrile episodes was identified in 91% of cases. The etiologic agent was determined in 46% of cases: virus predominated, followed by pneumonia. Septicemia was more frequent in children with active leukemia than in those in remission. In 44 febrile episodes the initial neutroph ils were not greater than 1,000/ul. Treatment consisted of methicillin and gentamicin, adding carbenicillin or trimethoprim-sulfamethoxazole in selected cases. The drugs were effective in 86% of febrile episodes. Of 12 children who died, 6 were leukemia-free at the time. (31 Refs) (In SPA)

78. HERPES SIMPLEX INFECTION IN ACUTE MYELOGENOUS LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES: A PROSPECTIVE STUDY.

Lam MT, Pazin GJ, Armstrong JA, Ho M
(c/o Ho), Univ. Pittsburgh, A427 Crabtree Hall, Pittsburgh, PA, 15261
Cancer; 48(10):2168-2171 1981

To better define the frequency and clinical characteristics of herpes simplex virus (HSV) infection in adult patients with acute myelogenous leukemia (AML), the authors prospectively studied 29 patients undergoing remission induction chemotherapy with twice weekly throat wash cultures for an av of 25.3 days. Ten seropositive patients (34.5%) shed HSV at least once. Eight patients were asymptomatic. Two episodes of herpes labialis were severe and persistent, but no visceral dissemination was observed. Reactivation of HSV infections in AML patients presumably with marked immunosuppression occurs, but less frequently and more benignly than has been suggested. Daunomycin and cytosine arabinoside, which can inhibit HSV replication, may have accounted for this lower frequency of reactivation. (Author abstract) (13 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

79. A HYPOTHESIS ON THE ETIOLOGY OF ADULT T-CELL LEUKEMIA/LYMPHOMA.

Tajima K, Tominaga S, Shimizu H, Suchi T
Div. Epidemiology, Aichi Cancer Center Res. Inst., 81-1159 Kanokoden, Tashiro-cho, Chikusa-ku, Nagoya 464, Japan
Gan; 72(5):684-691 1981

The results of the nationwide survey performed by the T- and B-cell Malignancy Study Group revealed that adult T-cell leukemia/lymphoma (ATLL) was prevalent in limited zones in Kyushu, mainly in coastal areas, warm in winter and humid in summer. It was found that the geographical distribution of filariasis was very similar to that of ATLL. It is known that filariasis affects lymphatic vessels and results in several lymphoreticular ailments, and microfilaria is transmitted by mosquitoes infected with some kinds of not yet fully identified viruses. From analyses of the time trends of the av wt and height of school children by prefecture, it is suggested that the nutritional condition of inhabitants in Kyushu might have been poorer than that of inhabitants of other areas in Japan, especially in the past. In order to elucidate the etiology of ATLL, relevant geographic-pathological information and other related information was accumulated and an etiological hypothesis was formulated. It was hypothesized that repeated exposure to filarial antigen and some viruses might have played an important role in the etiology of ATLL and that undernutrit ion had also contributed to the progression of ATLL. (Author abstract) (31 Refs)

SELECTED PRE-CLINICAL STUDIES

80. AN IN VITRO MODEL FOR ACUTE MYELOGENOUS LEUKEMIA CHEMOTHERAPY.

Koeffler HP, Yen J, Lowe L
Dept. Medicine, Center Health Sciences, Univ. California, Los Angeles, CA, 90024
Cancer; 48(9):1958-1963 1981

A human acute myelogenous leukemia cell line that forms colonies in soft-gel culture (KG-1) was used to test the effect of various schedules and combinations of chemotherapeutic agents. For comparison, the drug sensitivity of normal human marrow myeloid clonogenic cells was tested. Cytosine arabinoside inhibited both the KG-1 and normal human colony-forming cells (CFC) approx 25% after a 2-hr exposure, 50% after a 5-hr exposure, and 90% after a 24-hr exposure. Daunorubicin had nearly an equal cytotoxic effect on KG-1 and normal marrow CFC after a 2-to 72-hr exposure to the drug. Daunorubicin at 0.15 ug/ml produced nearly complete inhibition of colony-forming cells. Amphotericin B also inhibited colony formation. Amphotericin B and daunorubicin, when combined in culture, produced a synergistic suppression of normal and leukemic CFC. The antileukemic agent 5-azacytidine at a concentration of 0.1 ug/ml produced approx 60% inhibition of colony formation. Cytidine partially rescued CFC when the nucleoside was added in seven-fold excess to cultures containing 5-azacytidine. Leukemic and normal marrow clonogenic cells have nearly the same sensitivity to each chemotherapeutic agent and combination. Human acute myelogenous leukemia lines may provide useful models for the development of new chemotherapeutic schedules and combinations. (Author abstract) (47 Refs)

81. SYNTHESIS AND ANTITUMOR ACTIVITY OF AN ACYCLONUCLEOSIDE DERIVATIVE OF 5-FLUOROURACIL.

Rosowsky A, Kim SH, Wick M
Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 24(10):1177-1181 1981

The pyrimidine acyclonucleoside 5-fluoro-1-[(2-hydroxyethoxy)methyl]uracil (3) was synthesized as part of a program aimed at the development of new 5-fluorouracil derivatives with fewer side effects and a broader margin of safety. Condensation of 5-fluoro-2,4-bis[(trimethylsilyl)oxy]pyrimidine with 2-acetoxyethyl acetoxymethyl ether (6) in the presence of SnCl4 afforded the acetate ester 7, which on deprotection with NaOMe gave 3 in 50-60% overall yield. The 5-bromo and 5-iodo analogues 10 and 11, re-

spectively, were obtained similarly. Reaction of 5-fluoro-4-(methylthio)-2-[(trimethylsilyl) oxyl]pyrimidine with 2-acetoxyethyl acetoxymethyl ether and SnCl4, followed by ammonolysis, yielded 5-fluoro-1-[(2-hydroxyethoxy)methyl]cytosine (12). Deamination of 12 with nitrous acid produced 3, thereby confirming that alkylation of 5-fluoro-2,4-bis[(trimethylsilyl)oxy]pyrimidine had occurred at N1. The ID50 of 3 against L1210 mouse leukemia cells in culture was 1.7 x 10(-5) M, as compared with 1 x 10(-6) M for FU. The 5-fluorocytosine analogue 12 was inactive at up to 1 x 10(-4) M, and the other halogenated derivatives 10 and 11 had no effect even at 1 x 10(-3) M. When 3 was given ip in water to P388 leukemic mice at 400 mg/kg (bid x 4) or 240 mg/kg (qd 1-9), a 75% increase in survival was observed relative to untreated controls, and there was no evidence of any host toxicity. (Author abstract) (17 Refs)

82. THE EFFECT OF FRACTIONATED VERSUS UNFRACTIONATED TOTAL BODY IRRADIATION ON THE GROWTH OF THE BN ACUTE MYELOCYTIC LEUKEMIA.

Hagenbeek A, Martens AC

Bone Marrow Transplant Unit., U.C.I.A. Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024

Int J Radiat Oncol Biol Phys; 7(8):1075-1079 1981

The quantitative and qualitative effects of various total body irradiation (TBI) regimens in a rat acute myelocytic leukemia model (BNML) which shares many characteristics with human acute myelocyitc leukemia, with emphasis on tumor load reduction are described. The results of high dose rate (HDR) acute, and HDR fractionated TBI, and the efficacy of low dose rate (LDR) continuous TBI are also reported. The most important determinants of HDR TBI efficacy were the total radiation dose and the dose delivered per fraction, and the time interval between the fractions. In the LDR TBI group, more leukemic cells were killed at higher radiation doses. However, at the time termination of treatment with 2,000 cGray, 50% of the rats had died. The remaining rats in this group as well as those treated with lower radiation doses all died from leukemia. Unfractionated TBI (900 cGray HDR) appeared to be one of the most effective regimens in terms of reducing the tumor load. However, approx half of the rats were killed by radiation-induced toxicity. The calculation of the log cell kill from the prolongation of median life span was found to be a valid method for determining the efficacy of TBI. (12 Refs)

REVIEWS

83. A CRITICAL REVIEW OF THE LITERATURE ON HAIRY CELL LEUKEMIA. FIRST PART: DIAGNOSIS AND PROGRESSION.

Bernadou A

Centre de Diagnostic, Hotel Dieu, 1, place du Parvis Notre-Dame, 75181 Paris, France

Sem Hop Paris; 57(33-36):1366-1371 1981

Hairy cell leukemia (HCL) affects primarily men between 19 and 87 yr old with a median age of 53 yr. In 75% of cases, splenomegaly is associated with HCL. Cytopenias have been observed in 45-90% of patients with HCL. Other associated anomalies include the presence of a circulating mononuclear clear cell, myelofibrosis and leukemic infiltration of the bone marrow. Tartrate resistant acid phosphatase activity is diagnostic for HCL. Although the number of B and T lymphocytes are decreased in HCL, there does not seem to be any profound problems with humoral or cellular immunity. The diagnosis of HCL is often difficult. Medullary biopsy is the only test that is reliable in 70% of cases. Because of the associated neutropenia, the principal risk of HCL is infection. The cytopenia associated with HCL can often be successfully controlled with surgical treatment. Splenectomy has improved the median survival rate and the infectious risk in patients with HCL. The postoperative mortality rate has reached 15% following splenectomy for HCL. Other treatments used include symptomatic therapy, chemotherapy, and leukapheresis. (134 Refs) (In FRE)

84. A CRITICAL REVIEW OF THE LITERATURE ON HAIRY CELL LEUKEMIA. SECOND PART: THE ORIGIN OF THE HAIRY CELL.

Bernadou A

Centre de Diagnostic, Hotel-Dieu, 1, place du Parvis Notre-Dame, 75181 Paris, France

Sem Hop Paris; 57(33-36):1380-1385 1981

Studies on the cellular origin of hairy cell leukemia (HCL) are reviewed. Arguments for the monocyte origin of the hairy cell (HC) are questionable. These include morphologic, cytochemical, functional, and immunologic arguments. More recent and convincing studies have investigated the immunological aspects of the HC. The presence of a single type of surface immunoglobulin on the HC is a strong argument in favor of their B lymphocyte origin. Other findings supporting a B cell origin include intracytoplasmic immunoglobulin, secretions of immunoglobulin by the HC, the culture of HC leading to B or T cell markers, rosette formation with mouse red blood cells, and the association of HCL with paraproteinemias. Recent studies have indicated the T cell origin of HCL. Findings include rosette formation of T cell markers on HC, cytotoxicity of anti-T sera to HC, and the persistance of T cell markers on continuous lines of cultured HC. It is suggested that the HC arises from heterogeneous cell lines and that proliferative cells of different origins are responsible for HCL. (134 Refs) (In FRE)

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ICRDB CANCERGRAM

ACUTE AND CHRONIC LEUKEMIA

Diagnosis, Treatment

SERIES CT03 No. 82/04 APRIL, 1982

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DIAGNOSIS

1. COMPUTED TOMOGRAPHY BRAIN SCANS IN LONG TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

Esseltine DW, Freeman CR, Chevalier LM, Smith R, O'Gorman AM, Dube J, Whitehead VM, Nogrady MB
Div. Hematology, Montreal Children's Hosp., 2300 Tupper St., Montreal, Quebec, H3H 1P3, Canada
Med Pediatr Oncol; 9(5):429-438 1981

There have been varying frequencies cited for the occurrence of abnormal brain CT scans in leukemic patients and conflicting evidence about the significance of these abnormalities and their relationship to sanctuary therapy. Our study of CT brain scans in 26 long survivors of acute lymphoblastic leukemia showed an overall prevalence of 35% abnormal scans. There was no statistically significant differe nce between the

HE 20. 3173/2:

number of abnormal scans seen in patients given radiotherapy as part of their CNS prophylaxis and those receiving only intrathecal methotrexate. Because the children in each treatment group were evenly matched with respect to other treatment variables possibly relevant to the causation of abnormal brain scans, a strong case is made for more rigorous design of such studies, preferably in a prospective fashion, looking simultaneously at other parameters of brain structure and function. (Author abstract) (27 Refs)

2. CLINICAL ANALYSIS OF 21 CASES OF NERVOUS SYSTEM DAMAGE IN LEUKEMIA.

Wei G, Zhan Q, Xiao Z
Dept. Internal Neurology, Beying Second Medical Coll., Affiliated Xuanwu Hosp., Beijing, People's Republic of China
Zhonghua Yixue Zazhi; 60(4):212 1981

Diagnosis and clinical findings are described for 21 cases of acute leukemia (13 males, 8 females; aged 1.5-77 yr) infiltrating the nervous system. There were 12 cases of acute granulocytic leukemia, 7 cases of acute lymphocytic leukemia, 1 case of acute monocytic leukemia, and 1 case of unclassified acute leukemia. Based on site of infiltration, clinical manifestations, cerebrospinal fluid analysis, x-ray examination, electroencephalogram, and autopsy findings, nervous system damage can be classified into 5 types: (1) brain substance type (including intracranial hemorrhage), 12 cases; (2) brain meningeal type, 4 cases; (3) spinal cord type, 3 cases; (4) peripheral nerve type; and (5) chloroma type, 3 cases. Some of the nervous damages, especially those of the peripheral nerves, were of multiple occurrence. Over half of the cases (12) in this series had nervous system damages as primary or main symptoms, 5 of whom had been misdiagnosed as brain tumors. Reasons for this misdiagnosis are discussed. (no Refs) (In CHI)

3. FACTORS AFFECTING SURVIVAL OF PATIENTS WITH ACUTE MYELOCYTIC LEUKEMIA PRESENTING WITH HIGH WBC COUNTS.

Vaughan WP, Kimball AW, Karp JE, Dragon LH, Burke PJ
Johns Hopkins Oncology Center, Rm 3-109, 600 N Wolfe St., Baltimore, MD, 21205
Cancer Treat Rep; 65(11/12):1007-1013 1981

Eighteen patients referred to The Johns Hopkins Oncology Center for treatment of acute myelocytic leukemia during a 2-year period had pretreatment wbc counts greater than 50,000/ul. Despite immediate admission, aggressive supportive care, and rapid institution of chemotherapy, six patients died from complications of the high wbc count at presentation. The patients who died had significantly higher initial wbc counts, lower platelet counts, and lower arterial oxygen saturation; they were older, more likely to be female, and more likely to have abnormal serum urea nitrogen than the 12 patients who survived. Five of the six patients who died had experienced a delay of greater than 48 hours from diagnosis to referral , and only one of the 12 patients who survived was not promptly referred for treatment at the time of diagnosis ($p = 0.004$). A mathematical model, the logit of the fraction of the initial wbc count versus the logarithm of time after starting therapy, was used to describe the response of the wbc count to chemotherapy. This logit analysis reduced the data for individual patients to a linear function, permitting statistical description of the population as a whole. This statistical description makes possible the comparison of different approaches to lowering the wbc count in such patients and the correlation of rate of response of wbc count with the probability of achieving remission and with duration of remission. (Author abstract) (15 Refs)

4. CONTAMINATION OF CEREBROSPINAL FLUID SPECIMENS WITH HEMATOGENOUS BLASTS IN PATIENTS WITH LEUKEMIA.

Rohlfing MB, Barton TK, Bigner SH, Johnston WW
(c/o Johnston) Dept. Pathology, Duke Univ. Medical Center, Box 3712, Durham, NC, 27710
Acta Cytol (Baltimore); 25(6):611-615 1981

Hematogenous blasts in cytologic preparations of cerebrospinal fluid (CSF) have generally been thought to indicate leukemic involvement of the CNS. however, two leukemic patients who came to autopsy had no CNS involvement despite positive CSF preparations shortly before death. Both patients had over 10,000 blasts/cu mm in their peripheral blood. The CSF specimen from one patient was grossly bloody, but the specimen from the second patient was clear. An experiment was designed to test the hypothesis that membrane filter techniques are sufficiently sensitive to detect blasts in CSF contaminated by amounts of leukemic blood too small to be detected visually. Blood from a leukemic patient with 130,000 cells/cu mm was serially diluted in CSF from 1:20 to 1:1,600,000 and membrane filters from each dilution were examined. No blood could be detected visually at the 1:8,000 and further dilutions. Blasts forms were seen on membrane filter preparations down to the 1:1,600,000 dilution, which contained 0.000000125 ml of blood, equivalent to about 1/40,000th the vol of an 18-gauge spinal needle. These findings suggest that contamination of CSF specimens with minute amounts of blood, undetectable by visual inspection, may lead to erroneous interpretation of leukemic involvement of the CNS. (Author abstract) (6 Refs)

5. THE APPLICABILITY OF SIMPLE BLOOD AND BONE MARROW VARIABLES IN PREDICTION OF ACUTE LEUKAEMIA IN PATIENTS WITH ACQUIRED BI- OR PANCYTOPENIA.

Clemmesen L, Hansen MM, Mortensen L, Thiede T, Videbaek A
Ved Hojmosen 111, DK-2970 Horsholm, Denmark
Scand J Haematol; 27(3):193-200 1981

A retrospective study of 44 patients presenting with acquired bi- or pancytopenia (B/PC) and no evidence of any causal disorder was carried out. Twelve patients developed acute nonlymphobl astic leukemia after 2-51 mo. Compared to the nonleukemic subjects the preleukemic patients at the onset of B/PC had significantly higher counts of myeloblasts and other myelopoietic cells in the bone marrow, more cellular marrows due to more dense cellularities of all compartments, higher blood granulocyte and monocyte counts, more pronounced anisocytosis, and in some cases a small number of circulating myeloblasts. A stepwise multiple logistic regression analysis identified three combinations of variable displaying significant simultaneous association with subsequent leukemic transformation. Among these the combination of marrow myeloblast percentage and blood granulocyte count might be applicable to early prospective identification of patients with preleukemic B/PC. (Author abstract) (18 Refs)

6. MORPHOLOGICAL ALTERATIONS OF KIDNEYS IN THE COURSE OF LEUKEMIA AND THE PLASMA THROMBOPOIETIC ACTIVITY.

Kemona H, Kemona A
Zaklad Diagnostyki Klinicznej, Instytut Biochemii i Analityki Medycznej AM, ul. M. Sklodowskiej-Curie 24A, 15-276 Bialystok, Poland
Przegl Lek; 38(7):537-540 1981

Morphological changes of the kidneys and the plasma thrombopoietic activity were studied in an autopsy series of 21 patients with acute myeloid leukemia (AML), 25 patients with chronic myeloid leukemia (CML), and 24 patients with chronic lymphocytic leukemia (CLL). Highly pronounced leukemic infiltration of the kidneys was found in 14 patients with AML, 5 patients with CML, and 10 patients with CLL. The plasma thrombopoietic activity, determined by means of 75 Se-methionine and expressed as pulses/mg of platelet protein, was also lowest in the patients with AML: 470 +-85 pulses/mg, versus 650 +-140 pulses/mg in healthy controls, 580 +-105 pulses/m in the patients with CML, and 530 +-140 pulses/mg in the patients with CLL. The results indicate that renal lesions occur in the course of leukemia and that the kidney is the probable site of thrombopoietin production. (10 Refs) (In POL)

7. LONG-TERM SURVIVAL IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA IN ITALY.

Mandelli F, Amadori S, Ceci A, Guazzelli C, Madon E, Marchi A, Masera G, Paolucci G, Zanesco L
Inst. Hematology, Univ. Rome, Via Chieti-7, 00161 Roma, Italy
Cancer; 48(11):2364-2367 1981

Among 727 children with acute lymphocytic leukemia (ALL) observed at eight pediatric clinics in Italy in the yr 1967-1974, 200 (27.5%) survived for more than 5 yr after diagnosis. The proportion of long-term survivors rose significantly during the yr 1970-1974 when aggressive therapeutic programs with curative intent were uniformly adopted in Italy (19.8% vs 29.4%; p less than 0.05). Clinical and laboratory data at diagnosis of the 200 long-term survivors were analyzed and compared with that of the 527 nonsurvivors. We found that, besides a WBC count greater than 50,000 cells/mm3, other factors such as early C NS leukemia and the presence of mediastinal mass were predictive of a poorer prognosis for long-term survival. Life-table analysis revealed that the chance of long-term survival was significantly higher in those children who have survived for 5 yr without relapse (82.9% vs 24.1%; p less than 0.01). Although late initial relapse is always possible, if a child with ALL remains in continuous complete remission for at least 9 yr, it is likely that the patient is cured. (Author abstract) (20 Refs)

8. SPLENIC ALTERATIONS IN HAIRY CELL LEUKEMIA.

Pilon VA, Davey FR, Gordon GB
(c/o Davey) Div. Clinical Pathology, State Univ. New York, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210
Arch Pathol Lab Med; 105(11):577-581 1981

Spleens from 12 patients with hairy cell leukemia were studied for morphologic alterations. Paraffin-embedded, plastic-embedded, and fresh-frozen tissue sections were stained for a variety of histochemical reactions. Hairy cells were present in great numbers within the splenic sinuses and cords. Hairy cells adhered to splenic endothelial lining cells, other hairy cells, and RBC. Large clumps of hairy cells filled and partial occluded splenic sinuses. Numerous dilated sinuses, abnormal sinuses, and blood-filled spaces were present in all cases. Ring fibers around abnormal sinuses were fragmented and reduced in amount. Occasionally, the number of reticular fibers appeared increased around abnormal sinuses, but, in general, it was decreased in areas around the blood-filled spaces and in splenic cords markedly infiltrated by hairy cells. The formation of abnormal sinuses and blood-filled spaces probably resulted from the obstruction of venous blood flow and from injury or death of endothelial lining cells. (Author abstract) (24 Refs)

9. CYTOGENETICS IN THE ACUTE LEUKEMIAS.

Prieto F, Badia L, Castell V, Perez-Sirvent ML, Marty ML
Laboratorio de Genetica, Clinica Infantil, Ciudad Sanitaria de la Seguirdad Social 'La Fe', Avda. Campanar, 21, Valencia-9, Spain
Sangre (Barc); 26(5B):738-755 1981

Out of 64 cases of acute leukemia (47 non-lymphoblastic and 17 lymphoblastic ones) in which cytogenetic studies were performed, 30 had normal karyotype (22 non-lymphoblastic and 8 lymphoblastic). The acute non-lymphoblastic leukemias with normal karyotype had a mean survival close to 11 mo, as opposed to 2-1/2 mo for the cases in which all the leukemia cells had abnormal karyotypes. The nine patients with WBC count above 100,000/cu mm had survivals slightly over 4 mo in spite of the normal karyotype found in seven of them. Chromosome 8 trisomy was the commonest numeric alteration, and it was seen n both leukemia groups; t(8q-; 21q+) associated to loss of the Y chromosome was found in a patient with M2 non-lymphoblastic leukemia, and this represents a 2% frequency in the series. Two patients with L3 lymphoblastic leukemia showed the same structural alteration, t(8q-; 14q+); one of them had other cytogenetic anomalies including two acrocentric marker chromosomes comprised of genetic material from chromosome (1(q21 q44)) translocated into a Y gonosome. The similarity of both cases with those of Burkitt lymphoma from a clinical, cytological, and cytogenetic standpoint is further evidence in support of the identity of L3 lymphoblastic leukemia and Burkitt lymphoma, which could be regarded as different manifestations of a unique disease status. (Author abstract) (58 Refs) (In SPA)

10. PH1 CHROMOSOME IN CHRONIC MYELOID LEUKEMIA. DIAGNOSTIC AND PROGNOSTIC VALUE.

Labal de Vinuesa M, Brieux de Salum S
Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina
Medicina (B Aires); 41(3):293-296 1981

The 48 myeloproliferative patients were examined for presence of Ph1 chromosome and/or other chromosomal anomalies: aneuploidy, translocation or deletion. Bone marrow samples were used to analyze 11-20 metaphases/patient. Of 48 patients, 11 who were later diagnosed as myelosclerosis, had no Ph1 chromosome, but various non specific aneuploidies. Ph1 chromosome was found only in chronic myeloid leukemia (CML) patients in agreement with Sandberg. Of 37 CML patients, 31 were Ph1+ with translocation t (9; 22) and 6 Ph1-. Survival time as well as peripheral blood leukocytes and platelets were increased in Ph1 + patients. Change in karyotype of one Ph1- patient with uncommon t (12; 13) preceded by 2 mo clinical signs of blast crisis. The importance of cytogenetic study in CML diagnosis and prognosis was stressed. (14 Refs) (In SPA)

11. CLINICAL-HEMATOLOGICAL AND CYTOGENETIC PARALLELS IN CHRONIC MYELOID LEUKEMIA.

Frenkel' MA, Volkova MA, Fleishman EV, Prigozhina EL, Solov'eva EA
Clinical-Diagnostic Lab., All-Union Cancer Res. Center, Moscow, USSR
Ter Arkh; 53(9):20-25 1981

Results of comparative evaluation of morphological and cytochemical characteristics of blast cells are reported in a study of patients who had chronic myeloid leukemia (CML). Of 72 such patients studied, 20 had poorly differentiated blast cells, 26 showed myeloid differentiation of blast cells, 5 had promyelocytic variant of the blast crisis, 3 had monoblastic variant of the blast crisis, 2 had erythromegakaryocytic variant of the blast crisis, and 16 showed lymphoid differentiation of the blast cells. Karyotyping of blast cells was carried out in 40 of the patients. Additional aberration, involving chromosome 17, was detected in 2/11 patients with poorly differentiated variant, 12/16 with myeloblastic variant, and 1/2 with monoblastic variant. The most pronounced inhibition of hematopoiesis was observed in the patients with promyelocytic variant of CML. Of 20 patients with poorly differentiated CML, only 4 survived f or greater than 5 yr, compared with 9/26 for those with myeloblastic CML, 2/5 for those with promyelocytic CML, 0/3 for those with monoblastic CML, 1/2 for those with erythromegakaryocytic CML, and 7/16 for those with lymphoblastic CML. (29 Refs) (In RUS)

12. IMPLICATIONS OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY IN VARIOUS FORMS OF CHILDHOOD LEUKEMIA.

Welte K, Ebener U, Hinderfeld L, Ritter J, Henze G, Kornhuber B
Abteilung fur Padiatrische Hamatologie und Onkologie, Zentrum der Kinderheilkunde der Universitat, Theordor-Stern-Kai 7, 6000 Frankfurt/Main 70, W. Germany
Klin Paediatr; 193(3):165-171 1981

Mononuclear peripheral blood cells (pB) and bone marrow (BM) specimens from 63 children with acute leukemia were examined for terminal deoxynucleotidyl transferase (TdT) activity. TdT activity was 0.2 Units (U)/10(8) cells in normal specimens (pB and BM) and 1.2-60 U/10(8) in specimens from 49/52 acute lymphoblastic leukemia patients. B-cell leukemia was diagnosed in 2/3 of the remaining patients who were devoid of TdT activity. Elevated TdT activity was observed in only 1/11 acute non-lymphoblastic leukemia patients. In one acute leukemia patient, a TdT-positive lymphoblastic cell population was observed at diagnosis; 4 wk following therapy TdT-negative myeloblasts predominated. Of nine patients who were studied in the first 3 mo of remission, elevated TdT activity (2.5 U/10(8) cells) was observed in only one. The usefulness of TdT in the classification of acute leukemia is discussed. (46 Refs) (In GER)

13. TERMINAL TRANSFERASE EXPRESSION IN RELAPSED ACUTE MYELOID LEUKAEMIA.

Bradstock KF, Pizzolo G, Papageorgiou ES, Cetto GL, Prentice HG, Ganeshaguru K, Prentice AG, Smith A, Chilosi M, Ambrosetti A, Hoffbrand AV
(c/o Hoffbrand) Dept. Haematology, Royal Free Hosp., Hampstead, London NW3 2QG, England
Br J Haematol; 49(4):621-627 1981

In three cases of acute myeloid leukemia marked increases in expression of the nuclear enzyme, terminal deoxynucleotidyl transferase (TdT), were observed during disease relapse. The first case was heterogeneous at diagnosis, consisting of subpopulations of large TdT- myeloblasts and small TdT+ blasts; however, at relapse there was complete replacement by TdT+ lymphoblasts. The other cases at diagnosis were both typical acute myeloid leukemia, TdT-; at relapse, one showed a mixture of TdT- myeloblasts and TdT+ lymphoblasts, while in the other, TdT was demonstrated on a subpopulation of myeloblasts. No chromosomal abnormalities were found. It is suggested that in the first two cases these phenomena may have been due to leukemic involvement of a pluripotential stem cell, or that sub-clones with different properties may have coexisted. In the third case at relapse, TdT was expressed aberrantly by malignant myeloid cells. (Author abs tract) (26 Refs)

14. A SIMPLE TEST FOR THE TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE USING THE PEROXIDASE-ANTIPEROXIDASE TECHNIQUE.

Jager G
Abteilung Experimentelle Hamatologie, Gesellschaft fur Strahlen- und Umweltforschung Munchen, Landwehrstr. 61, D-8000 Munchen 2, W. Germany
Blut; 42(4):259-261 1981

A technique for detection of terminal deoxyribonucleotidyl transferase (Tdt), an enzyme marker for classification of acute lymphoblastic leukemias (ALL), is described. Cells of the Reh cell line were analyzed on a single-cell basis by the unlabeled antibody enzyme method. Mononuclear blood cells were used as controls. Results were compared with those from the immunofluorescence method. Incubation of slides at 37 C for 60 min followed by washing for 1 hr produced optimum results, with 83% of Reh cells being TdT-positive. No positive mononuclear cells or background staining were found under these conditions. The method tested offered the advantages of simplicity of necessary equipment, permanence of cell preparations, and the opportunity of counterstaining for morphological differentiation and quantitation of reaction product at the single-cell level. The method is recommended for routine classification of ALL. (5 Refs)

15. THYMIDINE KINASE ISOENZYMES IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Ellims PH, Gan TE, Van der Weyden MB
Monash Univ. Dept. Medicine, Alfred Hosp., Commercial Road, Prahran 3181, Victoria, Australia
Br J Haematol; 49(3):479-481 1981

The profile of thymidine kinase isoenzymes were determined in peripheral blood lymphocytes from 14 patients with chronic lymphocytic leukemia (CLL) and 31 controls. Twelve patients with indolent disease showed TK2 isoenzyme activity, while two patients in whom the disease evolved and two patients who presented with aggressive disease exhibited TK1 isoenzyme activity. The demonstration of TK1 activity in the peripheral blood lymphocytes of clinically aggressive CLL suggests that this isoenzyme may be a useful biochemical marker of such behavior. (Author abstract) (6 Refs)

16. USE OF THE TRITIATED THYMIDINE-LABELLING INDEX OF THE MYELOBLAST-PROMYELOCYTE POOL FOR THE IDENTIFICATION OF THE LEUKEMIC POPULATION IN OLIGOBLASTIC LEUKEMIA.

Seigneurin D, Hollard D
Laboratoire d'Hematologie, Centre Hospitalier Regional, Universitaire de Grenoble, F-38043 Grenoble Cedex, France
Acta Haematol (Basel); 66(3):181-186 1981

The bone marrow myeloblast-promyelocyte-labelling index of 32 patients with oligoblastic leukemia was studied at diagnosis and during the course of the disease. A low value (less than 0.17) or a decrease in the labelling index is suggestive of a poor prognosis with development into acute myeloblastic leukemia. Leukemic myeloblasts are characterized by their inability to differentiate and their low labelling index. The low labelling index or the decrease in this labelling index are, thus, an indication of an increase in the leukemic population. (Author abstract) (13 Refs)

17. COMPLEX CARBOHYDRATES AS DIFFERENTIATION MARKERS IN MALIGNANT BLOOD CELLS: GLYCOLIPIDS IN THE HUMAN LEUKEMIAS.

Klock JC, Macher BA, Lee WM, Greaves MJ, Lajtha L, Jasmin C, Bessis M, Ross D
1282 Moffitt Hosp., San Francisco, CA, 94143
Blood Cells; 7(2):247-255 1981

Cell surface glycolipids were studied in normal neutrophils and lymphocytes, chronic myelogenous and lymphocytic leukemia cells, and acute myelogenous and lymphoblastic leukemia cells. A few undifferentiated leukemias or leukemias of uncertain lineage were also studied. Glycolipids were extracted with thin layer and gas-liquid chromatography, gas chromatography-mass spectrometry, direct probe mass spectrometry, and enzyme treatment. Twenty glycolipids were identified and sequenced. Human WBC possess glycolipid patterns that distinguish them from other blood cells. Differences in glycolipids occur in WBC of myeloid and lymphoid types. Two main features emerge from study of glycolipids of human leukemic cells: (1) even though cells appear morphologically undifferentiated, all leukemias be classified as myeloid or lymphoid on the basis of their glycolipids; (2) complexity of cell surface glycolipids is positively correlated with their degree of morphological differentiation. No glycolipids were found in leukemic WBC which were not found in normal cells. Glycolipids may be useful as both cell- and differentiation-specific markers in human blood cells. Antigenic differences in human leukemic cells may partly be due to an altered distribution of complex carbohydrates at the cell surface. (11 Refs)

18. NEUTRAL GLYCOSPHINGOLIPIDS IN HAIRY CELL LEUKEMIA.

Lee WM, Klock JC, Macher BA
Cancer Res. Inst., Univ. California, Moffitt Hosp. M-1282, San Francisco, CA
Biochemistry; 20(22):6505-6508 1981

The neutral glycosphingolipids of hairy cells from a patient with hairy cell leukemia were chemically analyzed by thin-layer and gas-liquid chromatography, mass spectrometry, combined gas chromatography-mass spectrometry, and glycosidase treatment. These cells were found to have compounds containing one to four sugars. These compounds belong to the globo series of neutral glycosphingolipids and are similar to those found in human lymphocytes and chronic lymphocytic leukemia cells. They differ from the neutral glycosphingolipids found in human neutrophils and chronic myelogenous leukemia cells which are of the lactoneo and gala type. Neutral glycosphingolipids may be useful in classifying leukemias of uncertain origin. (Author abstract) (20 Refs)

19. PHOSPHOLIPID AND CHOLESTEROL DIFFERENCES AMONGST LEUKEMIC CELL TYPES WITH SPECIA L REFERENCE TO HAIRY CELL LEUKEMIA: A PRELIMINARY REPORT.

Golomb HM, Saffold CW, Nathans AH, Dawson G
Pritzker Sch. Medicine, Box 420, 950 E. 59th St., Chicago, IL, 60637
Clin Chim Acta; 116(3):311-318 1981

Amounts of whole cell cholesterol and phospholipids, as well as the types of phospholipids, were determined in 10 patients with the leukemic phase of hairy cell leukemia (HCL), compared with those in 15 patients with chronic lymphocytic leukemia (CML). Cholesterol was determined by the ferric chloride method, lipid phosphorus by the method of Ames and Dubin; values are reported as micromoles/10(8) whole cells. Mean values for cholesterol of malignant cells from HCL patients was 0.412 compared to 0.177 for CLL patients (p less than 0.001); phospholipid values were 0.746 and 0.469, respectively (p less than 0.001). Values for normal lymphocytes were 0.284 and 0.473, respectively. Thin-layer chromatography revealed the following percentages of phospholipid subtypes for HCL and CLL, respectively: sphingomyelin, 16.2 and 8.2%; phosphatidylcholine 46.0 and 55.1%. Differences were significant in both diseases (p less than 0.05). HCL cells are enriched two- or three-fold in sphingomyelin (on a micromole/g protein basis) at the expense of phosphatidylcholine compared to CLL cells. Increases in total cholesterol and phospholipid as well as in the selective portions of individual phospholipids could reflect and, possibly, result in the unique membrane architecture of the hairy cell. (15 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

20. SURFACE MEMBRANE CHARACTERISTICS AND CYTOCHEMISTRY OF THE ABNORMAL CELLS IN NONLYMPHOCYTIC LEUKEMIA.

Ikeda S
Dept. Hematology, Atomic Disease Inst., Nagasaki Univ., Sch. Medicine, Sakamoto-cho, Nagasaki 852, Japan
Nippon Naika Gakkai Zasshi; 70(4):553-564 1981

The surface membrane characteristics and cytochemistry of the leukemia cells were determined in 20 patients with acute myelogenous leukemia (AML), 2 with acute premyelogenous leukemia (APL), 3 with chronic myelogenous leukemia with malignant change (CMLC), 2 with acute monocytic leukemia (AMoL), 12 with acute-subacute myelogenous monocytic leukemia (MMoL) and with chronic myelogenous monocytic leukemia (CMMoL). The cells were examined for Fcgamma, Fcmu, C3b and C3d receptors by the percentage of rosette-forming cells by means of a microtest plate. Human group AB serum and AKR mouse serum were used as complement. Phagocytosis of the leukemia cells was also determined. Since most of the patients having cytoplasmic granules and peroxidase (PO) among the patients with AML and APL had Fcgamma or C3 receptors, the receptors, granules and PO were considered to appear simultaneously. CML (with malig-

nant change) patients had receptors although only a small amount of enzymes was expressed. All of the patients with AMoL and MMoL had seve ral receptors, and phagocytosis was also detected in all of the patients. Cytochemically, 5 of the 18 patients with AMoL, MMoL or CMMoL completely lacked alpha-naphthyl butyrate esterase in their monocytic leukemia cells, and 7 of the patients partially lacked this enzyme. Phagocytosis was detected in all of the patients, even those who lacked this enzyme. Therefore, the finding of immunological phagocytosis was considered valuable as evidence that a monocytic element constituted the leukemia cell. (20 Refs) (In JPN)

21. IMMUNOLOGICAL MONITORING OF RESIDUAL DISEASE IN TREATED THYMIC ACUTE LYMPHOBLASTIC LEUKEMIA.

Bradstock KF, Janossy G, Tidman N, Papageorgiou ES, Prentice HG, Willoughby M, Hoffbrand AV
Dept. Immunology, Royal Free Hosp. Sch. Medicine, Pond St., Hampstead, London NW3 2QG, England
Leuk Res; 5(4/5):301-308 1981

Lymphoid subpopulations of bone marrow (BM) in 18 patients (15 males, 3 females; 2-41 yr old) treated for thymic acute lymphoblastic leukemia (Thy-ALL) were analyzed to determine if residual leukemic lymphoblasts can be detected in patients considered to be in remission by conventional clinical and morphological data. There was initial response to cytotoxic therapy in each case. After 4 wk of therapy, BM samples were in morphological remission and contained less than 5% blasts. In two cases, however, the 4 wk remission BM samples were found to contain 5% cells expressing the human thymocyte/T cell antigen (HuTLA)+, immune region associated (Ia)-, terminal deoxynucleotidyl transferase (TdT)+ phenotype upon immunofluorescent examination (IF). This abnormal population became undetectable after further therapy. This phenotype was also found in four other patients. These observations indicated that IF technics can detect small numbers of HuTLA+, Ia-, TdT+ cells, characteristic of Thy-ALL, which were not evident morphologically. The HuTLA+, Ia-, TdT+ phenotype subsequently observed at relapse confirmed that these rare cells observed during remission were leukemic. In 10 other cases, Thy-ALL cells were not detected in remission BM. In 4/10 cases, no TdT+ cells were found. In the other six cases, 0.1-10% TdT+ cells were demonstrated; all were HuTLA- and the majority (53-85%) were Ia+. Relapse of Thy-ALL (with HuTLA+, TdT+, Ia- blasts) occurred in three of these patients 2-3 mo after detection of 0.2, 1.0, and 1.5% HuTLA-, Ia+, TdT+ putative normal cells, respectively. Two additional patients showed no Thy-ALL cells. Phenotypic shifts in Thy-ALL were examined. The results indicated that the indirect IF system using combinations of antisera to human differentiation-linked antigens is more sensitive for the identification of Thy-ALL than conventional morphological technics. (22 Refs)

22. USE OF IMMUNOLOGICAL METHODS IN CHARACTERIZING ACUTE LYMPHOBLASTIC LEUKEMIAS IN CHILDHOOD.

Cap J, Babusikova O, Misikova Z, Foltinova A
II. Detska klinika, Detska fakultna nemocnica, Dukl'anska 14, 881 25 Bratislava, Czechoslovakia
Bratisl Lek Listy; 76(2):183-191 1981

Spontaneous and immune rosette tests were performed in 47 children (3-14 yr old) with acute lymphoblastic leukemia (ALL). The tests were performed at the time of diagnosis in 26 cases, and during complete remission in the course of cytostatic therapy in 21. Immunological classification of ALL was possible in 16 cases: null cell type was found in 10 cases, B cell type in 2, T cell type in 1, and T + B cell type in 3. During the 4-30-mo follow-up period there were no differences in the course of the disease between the individual immunological types. Repeated rosette tests showed normalization of the T and B lymphocyte counts shortly after remission had been achieved. In the further course, the T cell count tended to decrease, reaching normal levels only after completion of the cytostatic therapy, while the B cell count remained within the normal range. (20 Refs) (In SLO)

23. COMPARISON OF SOME IMMUNOLOGICAL INDICATORS IN CHILDREN WITH FAVORABLE AND UNFAVORABLE COURSE OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Fabianova J, Mrackova E, Zavazal V
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Cesk Pediatr; 36(10):573-575 1981

Immunological indicators were studied in six children (4 boys and 2 girls, 3-12 yr old) with acute lymphoblastic leukemia (ALL), who were in first remission for at least 5 yr, and in eight other children (4 boys and 4 girls, 3-13 yr old) with ALL, who developed recurrences during the first yr of treatment and died 3-4 yr after diagnosis. All patients received remission induction therapy with the combination of prednisone (PR) and vincristine (VCR), methotrexate intrathecally and cranial irradiation, and maintenance therapy with MTX and and 6-mercaptopurine, and cyclic reinduction treatment with PR and VCR. The IgA, IgM, and IgA levels were within the normal range initially in the patients with favorable prognosis, and declined during the first and second yr of cytostatic therapy. While the IgA and IgG levels normalized from yr 3 onward, the IgM level remained low throughout the 5-yr follow-up period. The indicators of cellular immunity, assessed by skin tests and by determining the percentages of T and B lymphocytes, were within the normal range throughout the follow-up period. In the patients with unfavorable prognosis, the immunoglobulin levels were low throughout the follow-up period, and the indicator of cell-mediated immunity suggested a defect of T lymphocytes. (5 Refs) (In CZE)

24. CHARACTERIZATION OF THE PHYTOHEMAGGLUTININ-INDUCED PROLIFERATING LYMPHOCYTE SUBPOPULATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS USING A CLONOGENIC AGAR TECHNIQUE AND MONOCLONAL A NTIBODIES.

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Dept. Oncology/Hematology, Veterans Admin. Medical Center, East Orange, NJ, 07019
Blood; 58(5):1053-1055 1981

Peripheral blood lymphocytes from normal donors and patients with chronic lymphocytic leukemia, B-cell type, were purified into T, helper T, and suppressor T lymphocytes by fluorescence-activated cell sorting using OKT3, OKT4, and OKT8 monoclonal antibodies. The max response of the purified subpopulations to stimulation by phytohemagglutinin (PHA) was determined by measuring the production of colonies when the stimulated cells were grown on agar. The helper T cells in normal and CLL patients were the most responsive to PHA stimulation, although the responsiveness of helper T

cells to PHA was decreased in CLL. Purified CLL B cells responded minimally to PHA stimulation, but normal B lymphocytes did not. The abnormal response of CLL lymphocytes to PHA appears to be due to abnormal helper T cells, and, to a smaller extent, to the ability of CLL B lymphocytes to respond. (Author abstract) (17 Refs)

25. B LYMPHOCYTE FUNCTION IN B CELL CHRONIC LYMPHOCYTIC LEUKAEMIA.

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Br J Haematol; 49(3):395-403 1981

B-enriched lymphocyte populations from patients with chronic lymphocytic leukemia (CLL) were compared to B-enriched lymphocyte populations from normal age-matched controls for their ability to stimulate a proliferative response and to generate cytotoxic cells in allogeneic mixed lymphocyte cultures (MLC). The proliferative responses of MLCs were less than normal when the stimulating cells originated from B cells of patients with CLL. The degree of stimulation provided by the B cells from the patients with CLL inversely correlated with the peripheral white cell count. Lymphocytes from patients providing a poor stimulatory signal in the MLC tended to have less 'Ia-like' antigen than lymphocytes giving a moderate level of stimulation. B lymphocytes from patients with CLL which stimulated poorly in the MLC also failed to generate specific cytotoxic cells even when provided with a normal proliferative trigger. These data suggest that B lymphocytes from cases of CLL with markedly elevated WBC counts may have a diminished concentration of both 'Ia-like' and serum defined antigens. (Author abstract) (27 Refs)

26. IMMUNOLOGICAL STUDIES IN CHRONIC LYMPHOCYTIC LEUKEMIA. II. NATURAL KILLER- AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY POTENTIALS OF MALIGNANT AND NON-MALIGNANT LYMPHOCYTE SUBSETS AND THE EFFECT OF ALPHA-INTERFERON.

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Leuk Res; 5(4/5):349-355 1981

The effector cell potential of chronic lymphocytic leukemia (CLL) subsets was de termined in the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) assays. Lymphocyte subpopulations were isolated from peripheral blood obtained from 25 (43-76 yr old) CLL patients. The behavior of CLL cells in NK and ADCC assays was determined. Basic experimental conditions for the assays were determined. When unseparated lymphocytes from CLL patients were tested in NK (21 patients) and ADCC (25 patients) assays and compared to the cytotoxicities of 20 normal donors, the CLL cells were defective in both tests. The behavior of CLL cells in NK assays was defective with or without 1,000 IU alpha-interferon (AIF). The NK and ADCC defects were found mainly in the non-T fraction, while the T cells exhibited subnormal levels of lysis. By depleting the non-T cells of mouse rosette forming cells, a null cell subset was purified that exhibited considerable lysis in the NK test. AIF did not enhance ADCC by unfractionated CLL cells. When the NK activity of three CLL patients were tested against 7 target cell lines with NK sensitivities in normal donors ranging from very low to extremely, the same pattern was retained in the patients, although the addition of AIF tended to diminish the tendency by boosting the NK activity against the resistant lines proportionately more than against the sensitive ones. Compared with lysis by cells from normal donors, the lysis of cells from the patients, was still defective with all cell lines tested. (19 Refs)

27. DECREASED ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN VARIOUS TYPES OF LEUKEMIA IN MAN.

Jakobisiak M, Janowska-Wieczorek A, Dobaczewska H, Kantoch M, Marczak M, Oblakowski P, Lasek W, Sosnowska M
Dept. Transplantology, Inst. Biostructure, Medical Sch., Chalubinskiego 5, 02-004 Warsaw, Poland
Scand J Haematol; 27(3):181-185 1981

Antibody-dependent cellular cytotoxicity (ADCC) by cells from peripheral blood was studied in patients with: chronic lymphocytic leukemia (CLL), chronic granulocyte leukemia (CGL), acute lymphoblastic leukemia, acute non-lymphoid leukemia (ANLL) and compared with that of healthy donors. The ADCC activity in all the types of leukemia was on the average lower as compared with the control values, being especially low in both CLL and CGL. Further, it has also been shown that the ADCC activity of non-leukemic blood cells in ANLL was lower as compared with control values. The latter observation indicates that, at least in ANLL, the reduced ADCC potential of peripheral blood cells is not due to dilution of effector cells by poorly- or non-active leukemic cells. (Author abstract) (23 Refs)

28. THYMIC DYSFUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Ershler WB, Ney P, Britt J, Flynn B, Hong R
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Thymus; 3(4/5):203-212 1981

In order to delineate T-cell function in chronic lymphocytic leukemia (CLL), in vitro lymphocyte function was examined in 25 patients. The response to concanavalin A (con A) and pokeweed mitogen (PWM) was tested in 17 patients; response to phytohemagglutinin (PHA) was tested in 14 patients. Only one patient response was normal for PHA stimulation, one response was normal for con A stimulation, and three responses were normal for PWM stimulation, whether or not the patients had received chemotherapy. In recombination experiments, variable T- and/or B-cell defects as measured by PWM-stimulated proliferation were evident; the data demonstrated that in at least two and possibly three of the four patients tested, T-cell helper function was deficient. In only 2 of 22 patients tested did all three immunoglobulin class determinations fall in the normal range: IgG was normal in 10, IgA in 9, and IgM in 4 of the 22 samples tested. Immunoglobulin biosynthesis in two of four PWM-stimulated cultures was enhanced by incubation over cultured thymic epithelial monolayers. The studies make evident a profound deficiency in the in vitro response to mitogen stimulation in CLL; variable abnormalities in both B- and T-cell function exist in this disease. (23 Refs)

29. EXPRESSION OF RECEPTORS FOR IGA IN HAIRY-CELL AND OTHER B-CELL LEUKAEMIAS.

Lydyard PM, Powell RG, Fanger MW, Worman CP, Cawley JC
Dept. Immunology, Middlesex Hosp. Medical Sch., Arthur Stanley House, 40-50 Tottenham St., London W1P 9PG, England
Br J Haematol; 49(4):643-647 1981

In six cases of both hairy-cell leukemia (HCL) and chronic lymphocytic leukemia (CLL) it was shown that the pathologi-

cal cells express receptors for the Fc portion of IgA (RFcalpha). Many of the cells simultaneously expressed receptors for IgA, IgM and IgG, and blocking studies showed that these are distinct receptors. In contrast, the malignant cells of most of the various other B-cell leukemias studied showed low levels of RFcalpha expression. The significance of the results is briefly discussed and it is suggested that receptor expression may be a marker of certain stages of B-cell development. (Author abstract) (14 Refs)

30. PARTIAL NORMALIZATION OF B-CELL FUNCTION BY LEVAMISOLE IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Diez RA, Estevez ME, Sen L
Inst. Investigacious Hematologicas, Academia Nacional de Medicina, Las Heras 3092, Buenos Aires 1425, Argentina
Medicina (B Aires); 41(4):471-475 1981

The functional capacity of B lymphocytes induced by pokeweed mitogen (PWM) to differentiate into plasma cells was investigated in acute lymphoblastic leukemia (ALL) patients in continuous complete remission (CCR) with and without levamisole. Mononuclear cells were obtained from 15-20 ml of blood from each of 14 ALL patient receiving levamisole along with cytotoxic drugs and 7 ALL patients receiving cyt otoxic drugs only. Two million cells were treated with rabbit IgG antihuman total immunoglobin conjugated with fluorescein isothiocyanate and examined for surface immunoglobulin. Cells treated with PWM were incubated and examined for cytoplasmic immunoglobulin. Surface antigens were observed in 7.4% of normal patients and 5.4% of ALL patients. Cytoplasmic immunoglobulin in cells cultured with PWM were observed in 4.39% of normal patients, 2.34% of ALL patients receiving chemotherapy plus levamisole, and 0.17% in ALL patients receiving chemotherapy alone. Significantly lower differentiation ability was observed between normal patients and both groups of ALL patients. These results suggest that cytotoxic chemotherapy could induce an intrinsic defect in B cell ability to differentiate or interfere with plasma cell differentiation or regulation, and that levamisole is capable of partly correcting this defect. (18 Refs)

CHEMOTHERAPY

31. TREATMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA: RESULTS OF TWO TRIALS.

Koza I, Cerny V, Horak I, Bohunicky L, Gyarfas J, Svancarova L, Hal'ko J, Mardiak J, Zonnenschein T, Thalmeinerova Z
Inst. Clinical Oncology, 881 02 Bratislava, Czechoslovakia
Neoplasma; 28(4):473-484 1981

Thirty eight patients with acute lymphoblastic leukemia were treated with protocol 0171 (vincristine, prednisone(PRED), methotrexate(MTX), cyclophosphamide +-6-mercaptopurine (6-MP)) and protocol 0276/A (VRC, PRED, L-asparaginase, MTX, 6-MP, cyclophosphamide). Overall complete remission rate in both studies was 84-85%, and additional treatment in protocol 0171 resulted in complete remission rate of 92%. Median duration of complete remissions in protocol 0171 was 23 mo and median survival of all patients was 33 mo. Six patients randomized to regimen 'A' (without 6-MP in intensification) had median duration of complete remission 8 mo and median survival was 13 mo. Seventeen patients treated with regimen 'B' (with 6-MP in intensification) had median duration of complete remission 25 mo and median survival was 39 mo. Median survival of patients allocated on protocol 0276/A is 21+ mo and median duration of complete remission is 23 mo at present. Twelve percent of patients treated with the best regimen have survived more than 66 mo in continuous complete remission. The incidence of drug related death in complete responders was 6%. The relapses were most frequent during the first 2 yr of remission. Extramedullary leukemia as the initial site of relapse was observed in 9% of patients. (Author abstract) (23 Refs)

32. OUR EXPERIENCE IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA.

Pavlovsky S
Departamento de Onchohematologia, Instituto de Investigaciones Hematologicas, Pacheco de Melo, 3081, 1425 Buenos Aires, Argentina
Sangre (Barc); 26(5B):845-854 1981

We evaluated the results of the different treatment phases (induction, consolidation, CNS prevention and maintenance) in 1,200 acute lymphoblastic leukemias entered from 1967 to 1978 in four consecutive protocols of GATLA and evaluated in April 1981. We can conclude that: (1) WBC count and age are the major prognostic factors to be taken into account in any evaluation; (2) the triple combination DNM-VCR-PRED caused a significant increase in the percentages of complete remissions compared to VCR-PRED alone in children of high risk and adults; no differences were observed in children of low risk; (3) the methods of short consolidation with L-ASP as well as with CTX-AraC did not increase long term relapse free survivals; (4) the use of IT MTX-DMT during induction and maintenance was equally effective to radiotherapy in cranium and IT MTX-DMT in patients with less than 50,000 WBC count and slightly less effective in patients with more than 50,000 WBC count, however, this difference was not significant; (5) the use of daily 6MP and MTX twice weekly produced a significantly better survival free of disease than weekly 6MP and MTX. However, this treatment caused more myelosuppression and immunosuppression with higher percent of infectious episodes and deaths in complete remission; (6) the sequential reinduction treatment with VCR-PRED alternated with CTX-AraC produced a significantly higher survival free of disease in children of good prognosis; (7) levamisole treatment as adjuvant of maintenance chemotherapy caused a significantly higher survival free of disease than the control group, in patients of good and bad prognosis. (Author abstract) (13 Refs) (In SPA)

33. INTENSIFIED REMISSION INDUCTION THERAPY FOR ACUTE NONLYMPHOCYTIC (ANLL): TREATMENT REPORT ON 60 PATIENTS.

Urbanitz D, Buchner T, Kamanabroo D, Hiddemann W, Schulte H, Van de Loo J
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Blut; 43(2):129-133 1981

Sixty acute non-lymphocytic leukemia (ANLL) patients were treated with TAD, a high-dose drug combination including thioguanine, cytarabine, and daunorubicin. Median time from therapy initiation to remission was 31 days (range 23-95) for patients achieving complete remission (CR) after one cycle and 52 days (45-62) for those with CR after two cycles. The median time for recovery from severe cytopenia was 23 days (17-71) and 46 days (42-58), respectively. Adequate bone marrow reduction (less than 5%) occurred in 58/60 cases. Of the 15 patients who died during induction, 12 died within 6 wk

of therapy onset. Patients received a mean of 12.9 platelet/granulocyte transfusion during induction. Vomiting and diarrhea were common during induction; hypokalemia and hypoproteinemia were seen in 22% of induction cycles. Seventeen patients were in CR for 1+ to 22+ mo. Prospected median remission duration was 9.6 mo. Of all treated patients, 27 were alive 3-26+ mo and median survival was 11 mo. The six patients receiving two consolidation courses had a median remission duration of 19.1 mo (8.9-21.5) vs 3.6 mo (3.0-7.9) for seven patients, in whom any consolidation therapy had be omitted. A CR rate of 72% was achieved by intensified induction therapy in 60 adult patients with no age limitation. (7 Refs)

34. RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA AFTER ELECTIVE CESSATION OF INITIAL TREATMENT: FAILURE OF SUBSEQUENT TREATMENT WITH CYCLOPHOSPHAMIDE, CYTOSINE ARABINOSIDE, VINCRISTINE AND PREDNISONE (COAP).

Sallan SE, Hitchcock-Bryan S
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Med Pediatr Oncol; 9(5):455-462 1981

Although the majority of children with acute lymphoblastic leukemia (ALL) can electively stop treatment after 2-1/2-5 yr of continuous disease-free remission, 20-25% of those patients relapse after discontinuation of therapy. We treated 15 patients whose disease recurred after stopping treatment. Fourteen of them attained complete remission, but the median duration of disease-free survival was only 11 mo. In this population, the site of initial relapse, bone marrow or testicle, did not influence subsequent outcome. Patients who relapsed within 6 mo of stopping initial therapy had shorter second remissions than those who relapsed after 6 mo. We conclude that the combination chemotherapy utilized in this study was inadequate for the control of relapsed ALL. Future programs will have to use different drug combinations or bone marrow transplantation. (Author abstract) (24 Refs)

35. COMPARISON OF THE THERAPEUTIC RESPONSE OF PATIENTS WITH CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN RELAPSE TO VINDESINE VERSUS VINCRISTINE IN COMBINATION WITH PREDNISONE AND L-ASPARAGINASE: A PHASE III TRIAL.

Anderson J, Krivit W, Chilcote R, Pyesmany A, Chard R, Hammond D
Children's Cancer Study Group, 1821 Griffin Ave, Los Angeles, CA, 90031
Cancer Treat Rep; 65(11/12):1015-1019 1981

One hundred and seventy-nine previously treated children with acute lymphoblastic leukemia in relapse considered not 'resistant' to vincristine (VCR) were randomly allocated to receive reinduction therapy with either vindesine (VND) or VCR, in combination with prednisone and L-asparaginase. Complete remission rates were 57% for both regimens and were significantly greater for first relapsers (69%) than for subsequent relapsers (43%). No significant difference in response rates by regimen was observed within relapse groups. Patients treated with VND experienced significantly greater hematologic toxicity. These data suggest that there is no advantage to using VND instead of VCR in standard reinduction therap y for childhood acute lymphoblastic leukemia in relapse. (Author abstract) (11 Refs)

36. MUNICH ALL 77-01 STUDY OF TREATMENT OF ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDHOOD.

Haas RJ, Janka G, Netzel B, Helmig M
Kinderklinik der Universitat Munchen, Munchen, W. Germany
Klin Paediatr; 193(3):137-144 1981

Over a 3-yr period 104 children with acute lymphocytic leukemia (ALL) were treated in twelve clinics. An aggressive induction therapy was administered to achieve rapid max cell reduction. Therapy used prednisone (PRED), vincristine (VCR), adriamycin (ADM), and asparaginase. After remission was achieved, patients received methotrexate (MTX) infusion, cyclophosphamide, and cytosine arabinoside in an intensive phase. Cranial irradiation and intrathecal MTX were administered to protect the CNS. Long-term remission therapy included po 6-mercaptopurine and MTX. Half of the patients received reinduction therapy with PRED, VCR, and ADM. Complete remission was achieved in 93 cases. Two cases did not respond to treatment; two patients died during the induction phase. Relapse occurred within 4-39 mo in 27 cases. Seven patients died during remission. Probability of long-term remission after 36 was 68% for 86 patients. Reinduction therapy produced no apparent benefit. WBC count at diagnosis and T cell markers had significant prognostic value. The toxicity of the protocol requires its administration only in qualified centers. Findings subsequent to the study indicated toxicity can be reduced by administration of prophylactic antibiotics. (31 Refs) (In GER)

37. MANAGEMENT OF PATIENTS WITH ACUTE NON-LYMPHOCYTIC LEUKEMIA WHO FAIL FIRST CYCLE OF INDUCTION THERAPY.

Hasbrouck DJ, Peterson BA, Hurd DD, Bloomfield CD
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Leuk Res; 5(4/5):357-361 1981

The detection of refractoriness to chemotherapy following the initial treatment cycle was studied in 42 acute non-lymphocytic leukemia patients treated with adriamycin, cytarabine, and thioguanine with (37 patients) or without (5 patients) prednisone and vincristine. Six of the 42 patients died during initial induction. Of the 36 remaining patients, 22 achieved complete remission with one cycle of chemotherapy (CR-1), 7 with the second cycle (CR-2), and seven failed to achieve complete remission even after cycle 2 (NR). CR-1 and CR-2 were not significantly different from NR with regard to sex, age, bone marrow morphologic subtype or pretreatment Hb, platelet count, WBC count, percent peripheral blasts, absolute blast count, serum lysozyme level or bone marrow differential. These factors along with median pretreatment WBC count did not allow the identification of patients resistant to the regimens. In day 14 marrow, differential counts CR-2 and NR differed significantly; the median residual blast percentage in CR-2 and NR was 21 and 60, respectively (p less than 0.01). However, there was some overlap in their ranges. The median percentage of normoblasts also differed between CR-2 and NR (6 and 0, respectively, p less than 0.05) as did the median percentage of neutrophils and precursors (10 and 2, respectively, p less than 0.05). There was no overlap in the blast percentage in the day 21 marrow between CR-2 (median of 7, range of 2-27) and NR (median of 58, range of 35-93). CR-2 and NR also differed with regard to median percentage of normoblasts on day 21 bone marrow, being 8 and 2, respectively (p less than 0.01). The results indicated that patients with more than 30% blasts in their bone marrow 21 days after initiation of the first cycle

of chemotherapy should received an alternative regimen for their second cycle of induction therapy. (13 Refs)

38. HAIRY CELL LEUKEMIA WITH SEVERE BONE MARROW INSUFFICIENCY. COMPLETE REMISSION AFTER CHEMOTHERAPY IN TWO PATIENTS.

Marty M, Calvo F, Castaigne S, Flandrin G
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Nouv Presse Med; 10(36):2977-2979 1981

Two men (53-and 54-yr old) with hairy cell leukemia achieved complete remission following combined treatment with rubidazone (450 mg/square meter (m2) in 1 hr iv) on day 1, cytarabine (200 mg/m2/day, continuous iv) on days 1-5, 6-mercaptopurine (200 mg/m2/day), and cyclophosphamide (2,200 mg/m2 in 1 hr iv). Chemotherapy was initiated 24 hr after the begining of po antibiotics for intestinal decontamination. Parenteral nutrition (2,500 cal) was administered for 10 or 25 days. The indication for this therapy was severe neutropenia persisting for more than 2 mo, accompanied by infectious complications. Six and 3 mo after chemotherapy-induced aplasia, the two patients had normal peripheral blood and bone marrow biopsies showed the disappearance of hairy cells and bone marrow fibrosis. Despite these results, this chemotherapy regimen produced no improvements in patient comfort or survival. Indications for chemotherapy-induced aplasia in the treatment of hairy cell leukemia are discussed. The importance of a protected environment following such treatment is considered. (25 Refs) (In FRE)

39. TREATMENT OF REISTANT ACUTE LEUKAEMIAS. PROTOCOL I: NUTRITIONAL FACTORS PLUS CYTOSINE ARABINOSIDE. PROTOCOL II: NUTRITIONAL FACTORS PLUS CYTOSINE ARABINOSIDE PLUS ADRIAMYCIN.

Domingo-Albos A, Puig Zuza J, Alomar E, Gimferrer E, Brunet S, Palou L, Madoz P
Unitat d'Hematologia Clinica, Hosp. de la Santa Creu i Sant Pau, Avgda. S. Antoni Maria Claret, 167, Barcelona-25, Spain
Sangre (Barc); 26(5B):890-900 1981

Twenty-three patients suffering from different forms of acute leukemia and previously treated with several chemotherapy regimens were included in the present study. The Protocol I, based on a chemotherapy model proposed by Momparler, was comprised of nutritional factors and high doses of Ara-C alternately administered. The nutritional factors, including an amino acid mixture plus several vitamins, are intended to increase the proliferative activity of the leukemic cells so they become more sensitive to the cytotoxic effect of Ara-C. Of the 14 patients treated with this protocol, 4 achieved complete remission, all presenting acute myelogenous leukemia. Since the promyelocytic and lymphoblastic leukemias failed to respond to such therapy, the Protocol II was devised from the results attained with Protocol I. Protocol II included the nutritional factors plus Ara-C plus adriamycin. Nine patients with different acute leukemia types have hitherto received this variety, four complete and two partial remissions having been attained. Although the low number of patients included in Protocol II makes it impossible to draw definite conclusions, its effectiveness is seemingly superior to that of Protocol I, and its effects are exerted upon the acute lymphoblastic leukemias as well. The toxicity of both variants, in spite of the high Ara-C dosage, has been moderate. (Author abstract) (14 Refs) (In SPA)

40. EFFECTIVE REMISSION INDUCTION OF REFRACTORY CHILDHOOD ACUTE NONLYMPHOCYTIC LEUKEMIA BY VP-16-213 PLUS AZACITIDINE.

Look AT, Dahl GV, Kalwinsky D, Senzer N, Mason C, Rivera G
Div. Hematology-Oncology, St. Jude Children's Res. Hosp., PO Box 318, Memphis, TN, 38101
Cancer Treat Rep; 65(11/12):995-999 1981

Thirty-eight children and young adults with advanced acute nonlymphocytic leukemia (ANLL) in relapse were treated with VP-16-213 plus azacitidine (5AZ). Each patient had previously received many chemotherapeutic drugs, including anthracyclines and cytarabine. Initially, 16 patients received a 5-day course of VP-16-213 (100 mg/m2) daily x 3 days and 5AZ (150 mg/m2) daily x 2 days, repeated after 9-16 days. Since this treatment produced marrow hypoplasia and complete remission (CR) in only 1 of 16 patients, a more intensive regimen was devised: the remaining 22 patients received a course of VP-16-213 (200 mg/m2) daily x 3 days, followed by 5AZ (300 mg/m2) daily x 2 days, repeated after 1-2 days until the bone marrow became hypoplastic. After two to four courses, 18 patients had marrow hypoplasia and 10 of these achieved CR. The proportion of patients achieving CR with the higher doses was significantly greater than that with the initial doses (p less than or equal to 0.05). The toxicity also increased with the higher doses, with major problems due to prolonged pancytopenia. Supportive therapy was required for severe bleeding and infections. We conclude that the intensive treatment with VP-16-213 plus 5AZ can effectively induce remission in patients with refractory advanced acute nonlymphocytic leukemia. (Author abstract) (24 Refs)

41. THE BFM 76/79 ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY STUDY.

Henze G, Langermann HJ, Bramswig J, Breu H, Gadner H, Schellong G, Welte K, Riehm H
Kinderklinik, Freien Universitat, Heubnerweg 6, 1000 Berlin 19, W. Germany
Klin Paediatr; 193(3):145-154 1981

In the BFM 76/79 study, an attempt was made to improve the prognosis for children and adolescents with acute lymphoblastic leukemia at high risk for relapse [risk index (RI) greater than 3] by adaptation of therapy. The study included 158 patients. The results of BFM 76/79 and BFM 70/76 (historical control) studies were compared. All patients underwent combination chemotherapy (Protocol I). In patients with a RI less than 3, Protocol I was followed by maintenance therapy with po 6-mercaptopurine and methotrexate plus prednisone/vincristine reinduction pulses up to a total duration of 2 yr after diagnosis. High risk patients underwent 6-wk reinduction therapy (Protocol II) 4 or 20 wk after completion of Protocol II. The same maintenance therapy as above was administered for a total duration of 2.5 yr after diagnosis. A 70% disease-free survival was found for the entire group at 51 mo. Patients with a RI less than 3 showed no demonstrable difference in survival when compared with controls. In patients with an RI greater than 3 the prognosis was improved by 30% in the BFM 76/79 patients as compared with controls. Prognostic factors included initial peripheral blast cell count in the BFM 70/76 study, age greater than 10 yr in the BFM 76/79 study, and liver and spleen enlargement in both studies. The results indicated that intensification of therapy improves the survival of high-risk patients. (28 Refs) (In GER)

42. A PHASE I AND II STUDY OF M-AMSA IN ACUTE LEUKEMIA.

Slevin ML, Shannon MS, Prentice HG, Goldman AJ, Lister TA
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Cancer Chemother Pharmacol; 6(2):137-140 1981

The activity of 4'-(9-acridinylamino)-methanesulfon-m-anisidide (m-AMSA) in acute leukemia patients with relapsed [18 acute myeloblastic leukemia (AML): 7 males, 11 females; 17-69 yr old] and refractory [9 acute lymphoblastic leukemia (ALL): 8 males, 1 female; 2.5-47] acute leukemia, and as initial therapy in the myeloid blastic crisis of chronic myeloid leukemia (5 CML blast crisis: 2 males, 3 females; 23-52 yr old) was assessed in a Phase I/II study. m-AMSA was administered in 500 ml 5% dextrose water as an iv infusion over 1-2 hr for 5 days; the cycle was repeated approx every 21 days. Sixteen patients received 50 mg/square meter (m2), 5 patients 75 mg/m2, 11 patients 100 mg/m2, and 12 patients 150 mg/m2. Complete remission was achieved in 3/18 AML patients, 2/9 ALL patients, and 0/5 CML blast crisis patients. Partial remission was noted in 6/18 patients with AML, 4/9 with ALL, and 2/5 with CML blast crisis. The complete remissions all occurred with the 100 or 150 mg/m2 m-AMSA dose; 4/5 complete remitters received 150 mg/m2, 1/5 complete remitters received 150 mg/m2, and 1/5 received 100 mg/m2. Partial remissions were seen at lower doses. Hematological toxicity occurred in all patients and was dose-related. Nausea occurred in 32% and vomiting in 18% of courses and was generally mild and easily controlled. Stomatitis was noted in 8% of the courses at 50 mg/m2, but in 50% of courses at 150 mg/m2. No evidence of renal failure was observed. One patient died with clinical and post-mortem evidence of cardiac failure after one m-AMSA course. Results confirmed that m-AMSA is an active drug in AML and ALL. (5 Refs)

43. EFFECT OF HIGH DOSE BUSULPHAN ON LEUKAEMIC PROGENITOR CELLS IN CHRONIC MYELOID LEUKAEMIA.

Morstyn G, Sullivan J, Fairhead S, Cowling D, Hurley T
Walter and Eliza Hall Inst. Medical Res., Post Office, Royal Melbourne Hosp., Victoria 3050, Australia
Aust NZ J Med; 11(6):609-614 1981

Six patients with Philadelphia positive chronic myeloid leukemia (CML) were treated with single high doses of busulphan. The action of busulphan on the in vivo kinetics of circulating progenitor cells (colony forming cells) was measured using an agar culture system which involved scoring of total colonies and clusters at 7 days and of granulocyte, monocyte and eosinophil colonies at 14 days. High dose busulphan was found to be effective in suppressing circulating granulocyte, monocyte and eosinophil progenitor cells. The effect of busulphan on progenitor cells was rapid and their levels fell by at least 83% within 5 days. By contrast, the WBC fell by only 9% and the platelets fell by 10% over this time. Subsequently, the white cell count and platelet count fell to near normal levels. The progenitor cell levels began to rise again at a mean of 35 days following busulphan treatment and the WBC at a mean of 39 days in four patients. One patient remained in hematological remission for 6 mo following 100 mg of busulphan with less than 1 progenitor per 5 x 10(5) peripheral blood nucleated cells. One patient in myeloblastic transformation had a previously not described culture pattern consisting of a high cluster to colony ratio at 7 days and of an increased number of predominantly eosinophilic colonies at 14 days. There was no significant fall in progenitor cell levels following busulphan and this patient died. (Author abstract) (17 Refs)

44. THERAPEUTIC SELECTIVITY OF AND PREDICTION OF RESPONSE TO 2'-DEOXYCOFORMYCIN IN ACUTE LEUKAEMIA.

Prentice HG, Lee N, Blacklock H, Smyth JF, Kussell NH, Ganeshaguru K, Piga A, Hoffbrand AV
Dept. Hematology, Royal Free Hosp., Pond St., London NW3 2QG, England
Lancet; 2(8258):1250-1254 1981

Seventeen patients with acute leukemia refractory to conventional chemotherapeutic agents were treated with the adenosine deaminase inhibitor, 2'-deoxycoformycin (dCF). Of the twelve patients with acute lymphoblastic leukemia of the thymic phenotype (Thy-ALL), 7 went into complete remission after one or two courses of therapy. Two other (Thy-ALL) patients showed good partial response, and three were resistant to dCF. The five patients with acute leukemia of other phenotypes had progression of disease despite treatment with dCF. Response to dCF can be predicted from the pattern of change in cellular nucleotide levels in blood and/or bone marrow blasts which have been treated in vitro with dCF and deoxyadenosine. The main adverse effects of dCF therapy were renal and liver dysfunction, conjunctivitis, and hemolysis. (Author abstract) (22 Refs)

45. LOW-DOSE ADRIAMYCIN REMISSION MAINTENANCE FOR ADVANCED ACUTE LYMPHOBLASTIC LEUKEMIA: A SOUTHWEST ONCOLOGY GROUP STUDY.

Hvizdala E, Komp D, Ragab A, Crist W, Chu JY
Pediatric Oncology Group, Operation Office, 4386 Lindell Blvd., St. Louis, MO, 63108
Med Pediatr Oncol; 9(5):477-482 1981

A low-dose maintenance schedule of adriamycin was evaluated in children with advanced acute lymphoblastic leukemia. Thirty-six evaluable patients who achieved two or more remissions were given adriamycin, 10 mg/m2/wk, as a single maintenance agent. The median duration of second remission was 17 wk, but only 5 wk for third and fourth remission. Although the therapy was not found effective in more advanced disease, the median duration of second remission approached that obtained from various multi-agent treatment schedules. We conclude that the therapeutic efficacy of this treatment schedule makes it appealing for incorporation into multi-drug combination regimens. (Author abstract) (13 Refs)

46. SYNERGISTIC ACTION OF TWO POLYAMINE ANTIMETABOLITES LEADS TO A RAPID THERAPEUTIC RESPONSE IN CHILDHOOD LEUKEMIA.

Siimes M, Seppanen P, Alhonen-Hongisto L, Janne J
Children's Hosp., Univ. Helsinki, SF-00290 Helsinki 29, Finland
Int J Cancer; 28(5):567-570 1981

Sequential administration of alpha-difluoromethyl ornithine and methylglyoxal bis(guanylhydrazone), two differently acting inhibitors of the biosynthesis of natural polyamines, produced a rapid and distinct therapeutic response in four children with advanced lymphoblastic and in one with myeloblastic leukemia. The synergism between the action of the two compounds was based upon a unique drug interaction; a preceding treatment with difluoromethyl ornithine greatly increased the uptake of subsequently administered methylglyoxal bis(guanylhydrazone) as verified by the actual determinations of the latter drug in the circulating leukemia cells. The side-

effects associated with the combined drug regimen were either absent or mild. (Author abstract) (13 Refs)

RADIOTHERAPY

47. DECLINES IN IQ SCORES AND COGNITIVE DYSFUNCTIONS IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKAEMIA TREATED WITH CRANIAL IRRADIATION.

Meadows AT, Massari DJ, Fergusson J, Gordon J, Littman P, Moss K
Children's Hosp. Philadelphia, 34th and Civic Center Blvd., Philadelphia, PA, 19104
Lancet; 2(8254):1015-1018 1981

Intellectual and other neuropsychological dysfunctions have been observed in survivors of childhood acute lymphocytic leukemia (ALL). The possible relationship of therapy to these dysfunctions was investigated in a prospective study of children with newly diagnosed ALL seen at the Children's Hospital of Philadelphia. They were evaluated with standardized intelligence tests during the first mo of treatment and periodically thereafter. There were two therapy schedules - one using standard drugs for induction and maintenance, the other a more intensive schedule. CNS prophylaxis (2,400 rad cranial radiation and 6 doses of intrathecal methotrexate) was given to all. Significant reductions were found in overall IQ score for the majority of children, younger patients being most affected. More extensive testing of surviving children, with and without decline in IQ all of whom were normal on the first test, revealed patterns of functional deficits and residual strengths that could not be characterized with IQ testing alone. These deficits, which could affect learning and academic performance, were not seen in six children studied yr after receiving similar chemotherapy that included intrathecal and oral methotrexate but not cranial irradiation. (Author abstract) (24 Refs)

MULTIMODAL THERAPY

48. GLUCOCORTICOID RECEPTORS AND SENSITIVITY IN LEUKEMIAS.

Ho AD, Hunstein W, Schmid W
Medizinische Universitats-Poliklinik, Hospitalstrasse 3, D-6900 Heidelberg, W. Germany
Blut; 42(3):183-190 1981

Possible correlation between glucocorticoid receptor (GCR) determination and response to treatment in leukemias and lymphomas was studied. GCR determinations were made for leukemic cells from 46 adult leukemia patients and lymphocytes from 18 healthy controls. Leukemias included 17 acute nonlymphoblastic leukemias (ANLL), 4 acute lymphoblastic or undifferentiated leukemias (ALL/AUL), 3 blast crises, 15 chronic lymphocytic leukemias (CLL), and 7 leukemic malignant lymphomas (NHL). Normal lymphocytes expressed 2,312-6,856 GCR/cell (median 3,875). ANLL blasts had 0-15,295 GRC/cell (median 7,250). Two ALL/AUL patients with greater than 5,000 GRC/cell responded to combination therapy including glucocorticoids (GC); two ALL/AUL patients with less than 5,000 GRC/cell showed no response. CLL patients resistant to combination therapy including GC had generally lower GRC than responsive patients, indicating that GCR might have predictive value in CLL. No correlation was found between GCR and in vitro response to dexamethasone. No predictive value for GCR determination was indicated for nonlymphoid leukemias. (28 Refs)

49. BUFFY COAT AUTOGRAFTS FOR PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA IN TRANSFORMATION.

Goldman JM, Catovsky D, Goolden AW, Johnson SA, Galton DA
MRC Leukaemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 OHS, England
Blut; 42(3):149-155 1981

Twenty patients with chronic granulocytic leukemia (CGL) in transformation were treated with cytotoxic drug alone or cytotoxic drugs with whole-body irradiation (TBI) followed by transfusion of autologous buffy coat cells collected at diagnosis and stored in liquid nitrogen. All patients received one course of treatment with daunorubicin or adriamycin, cytosine arabinoside, 6-thioguanine, and sometimes etoposide (RATE). Group A (eight patients) received a second course of RATE or melphalan at high dosage (200 mg/square meter). Group B (four patients) received high dose cyclophosphamide (CP: 60 mg/kg x 2) followed by intermediate-dose TBI (600-900 rads). Group C (eight patients) received high-dose CP followed by high-dose TBI (1,000-2,000 rads). Cell grafts in all three groups consisted of a mean 25.1 x 10(8) cells/kg. Chronic phase hemopoiesis was restored in 19 patients. Recurrence of transformation occurred in 14 patients, of whom 1 is still alive. Mean survival time for 18 patients w died was 24 wk. Median survival time for all patients after grafting was 14 wk. One patient was alive in second chronic phase after 52 wk. One patient with a successful graft died of apparent host-versus-graft disease. Autografting evidently is useful as a palliative measure in some, but not all, cases of CGL in transformation. (16 Refs)

50. IMMUNOTHERAPY OF ACUTE LEUKEMIA PATIENTS.

Riabov NV, Riabova TI, Voronchikhina LD, Klestova VI, Bykova LI
Res. Inst. Blood Transfusion, Kirov, USSR
Sov Med; (8):21-25 1981

Efficacy of active immunotherapy (AIT: nonviable allogeneic leukemic cells, im) was evaluated in 100 acute leukemia patients (52 children and 48 adults). Histologically, 70 had acute lymphoblastic leukemia (ALL) and 30 had acute myeloblastic leukemia (AML). Among these patients, 50 received chemotherapy in combination with AIT and 50 received chemotherapy alone (controls). Rates of remission were 63% and 50%, respectively, in the ALL and AML adults who were administered the combined therapy, compared with 62% and 18% in corresponding controls. The rates were 85% in the ALL children and also 85% in the AML children administered the combined therapy, compared with 74% and 0% in controls. Av durations of survival of the adult ALL and AML patients administered the combined therapy were 22 mo and 9.6 mo, respectively, compared with 11.5 mo and 4.4 mo in controls. Av durations of survival in ALL and AML children administered therapy were 22 mo and 15.4 mo, respectively, compared with 14.8 mo and 6 mo in controls. (8 Refs) (In RUS)

SUPPORTIVE CARE

51. CYTOGENETIC CONVERSION FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ADVANCED CHRONIC MYELOGENOUS LEUKEMIA.

McGlave PB, Miller WJ, Hurd DD, Arthur DC, Kim T
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Blood; 58(5):1050-1052 1981

We performed a pilot study to test the effectiveness of allogeneic bone marrow transplantation in the treatment of chronic myelogenous leukemia. Five patients in the advanced stages of chronic myelogenous leukemia (4 in blast crisis, 1 in accelerated phase) with abnormal chromosomes underwent matched-sibling allogeneic bone marrow transplantation after preparation with busulfan, vincristine, cyclophosphamide, and fractionated total body irradiation. Engraftment and conversion to normal chromosome patterns after transplantation occurred in all five patients. None of the patients reverted to an abnormal chromosome pattern or demonstrated clinical or hematologic evidence of recurrent disease during the course of this study; however, longest survival from transplant was 248 days. Allogeneic bone marrow transplantation can eradicate the abnormal clone even in far advanced chronic myelogenous leukemia and can provide normal hematopoiesis. We suggest that clinical complications of chemotherapeutic toxicity and infection were responsible for the short survival in this group of patients, and that these complications could be decreased by performing transplantation in the chronic phase or early accelerated phase of the disease. (Author abstract) (11 Refs)

52. AUTOLOGOUS BONE MARROW TRANSPLANTATION.

Netzel B, Haas RJ, Rodt H
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Klin Paediatr; 193(3):279-283 1981

The use of autologous bone marrow obtained from children in remission from acute lymphatic leukemia to re-establish normal hemopoiesis after conditioning for relapse with high doses of chemotherapy and radiotherapy is described. The cells removed (1.9-7.4 x 10(8)/kg) were treated to destroy any residual tumor cells and preserved at-196 C for 1-48 mo. The stem cell viability of the reference samples was 80-100% following cryopreservation. Two patients in hematological relapse received cryopreserved cells. A 7-yr-old girl, in 3rd relapse was transplanted with 1.9 x 10(8)/kg cryopreserved nuclear bone marrow cells. Complete hematopoietic recovery and a 6-mo remission were obtained. An 8-yr-old boy in 3rd relapse received 3.7 x 10(8)/kg cryopreserved (12 mo) nuclear bone marrow cells. On day 7 after transpl ant, the patient died of cardiac complications. At that time, an early differentiation of normal myelopoiesis and erythropoiesis and no leukemic cells were found. The results indicated that bone marrow cells collected during remission and treated with antileukemic antisera can repopulate bone marrow and effect hematopoietic regeneration. (19 Refs) (In GER)

53. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHRONIC GRANULOCYTIC LEUKEMIA.

Doney KC, Buckner CD, Thomas ED, Sanders TJ, Clift RA, Hansen JA, Sale GE, Singer J, Storb R
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Exp Hematol; 9(10):966-971 1981

Eighteen patients with chronic granulocytic leukemia underwent allogeneic marrow transplantation from HLA-identical sibling donors. The preparative regimen included cyclophosphamide and 1,000-1,500 rad total body irradiation in either single or fractionated doses. Eleven patients were transplanted in blast crisis. One died too early to evaluate. Five had recurrent leukemia, three died of interstitial pneumonia (IP), and two are living in remission after 20 and 39 mo. One additional patient with blast crisis was transplanted while in remission after chemotherapy and is living in remission 28 mo after transplantation. Two patients were transplanted in the accelerated phase; one died early of infection and one died of IP. Four were transplanted in the chronic phase; one died of IP, one with graft-versus-host disease, and two are living in remission 11 and 25 mo after transplantation. (Author abstract) (14 Refs)

54. THE APPLICATION OF HOMOLOGOUS BONE MARROW TRANSPLANTATION IN ACUTE LEUKEMIA.

Lu D, Wang D, Yang S, Zhao S, Qiu J, Liu X
Dept. Internal Medicine, Affiliated Peoples' Hosp., Beijing Medical Coll., Beijing, Peoples' Republic of China
Zhonghua Neike Zazhi; 20(5):282-285 1981

Homologous bone marrow transplantation for the treatment of acute leukemia complicated with serious infections is described for 10 cases (5 males, 5 females; 14-52 yr old). There were nine cases of acute nonlymphocytic leukemia (including acute granulocytic leukemia, acute monocytic leukemia, and erythroleukemia) and one case of acute lymphocytic leukemia. Eight cases in this series were treated for the first time. Treatment consisted of chemotherapy (corticoids, vincristine, harringtonine, asparaginase, etc) followed by bone marrow transplantation. The control group consisted of 25 cases (14 males, 11 females; 15-60 yr old) of acute leukemia undergoing first treatment. The treatment method was the same except no bone marrow transplantation was given. After treatment, complete remission was observed in nine cases and partial remission in one case in the marrow transplantation group; there was no mortality during the remission-induction period. In contrast, complete remission was achieved in only nine cases and partial remission in two cases in the controls; there were also 14 deaths in this group. Two illustrative cases are detailed. It was concluded that bone marrow transplantation is effective in the maintenance treatment of acute leukemia complicated by serious infections. (11 Refs) (In CHI)

55. MARROW TRANSPLANTATION FOR CHILDREN WITH ACUTE NONLYMPHOBLASTIC LEUKEMIA IN FIRST REMISSION.

Sanders JE, Thomas ED, Seattle Marrow Transplant Group
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Med Pediatr Oncol; 9(5):423-427 1981

Thirteen children between the ages of 2 and 17 yr with acute nonlymphoblastic leukemia in first remission were transplanted from HLA matched sibling donors. They were transplanted at a median of 4 mo [2-8] following diagnosis. The preparative regimen of cyclophosphamide and total body irradia-

tion was well tolerated. Two patients died of pneumonia 66 and 94 days following transplant. One patient relapsed at 431 days, and died of leukemia at 490 days. Ten are living in remission 20-53 mo following transplantation. None are on maintenance chemotherapy, and all lead normal lives. As yet, growth is not impaired. (Author abstract) (19 Refs)

56. HLA AND BONE MARROW TRANSPLANTATION (BMT).

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Klin Paediatr; 193(3):266-271 1981

The survival rate after bone marrow transplantation (BMT) is discussed in relation to human leukocyte antigen (HLA) compatibility. The survival rate after BMT from an HLA-genotypically identical sibling in acute leukemia, combined severe immunodeficiency (SCID), and severe aplastic anemia patients was 56%, 55%, and 67/83%, respectively. When HLA-D identical related or unrelated donors were used, the survival rate for SCID patients was 37% in comparison with 18% for acute leukemia patients and 11% for aplastic anemia patients receiving bone marrow from HLA-phenotypically identical or HLA-D identical donors. Patients grafted with bone marrow from HLA-phenotypically identical unrelated donors died. All of the patients grafted with HLA-different marrow died. Patient survival depended on histocompatibility of donor and recipient, clinical treatment, and disease type of patient. Pre-BMT blood transfusion-induced sensitization seemed to decrease the BMT success in patients with severe aplastic anemia; BMT in acute leukemia patients in remission was more successful. (47 Refs) (In GER)

57. INITIAL TREATMENT OF ACUTE CHILDHOOD LEUKEMIA WITH EXTREME LEUKOCYTOSIS BY BLOOD EXCHANGE TRANSFUSION: RHEOLOGICAL ASPECTS.

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Klin Paediatr; 193(3):172-176 1981

The effect of exchange transfusion was studied in leukemic patients with extremely high leukocytosis. In these patients, the great number of poorly deformable lymphoblasts compared to normally deformable RBC influences the flow properties of leukemic blood leading to a greater possibility of leukostasis and bleeding. Removal of large amounts of leukemic cells by exchange transfusion with fresh blood decreased the leukemic cell burden, reduced the initially elevated WBC counts by more than 50% in three patients, improved anemia and thrombocytopenia, and normalized disturbed plasma coagulation. One patient with additional risk factors who was treated by exchange transfusion died 8 mo after diagnosis in hematologic relapse. No relapse was reported in the other two patients 6 and 9 mo after diagnosis. The results suggested that exchange transfusion with 150 ml/kg fresh blood is valuable in the prevention of early complications and the correction of hematological and rheological abnormalities in childhood leukemia with extreme leukocytosis. (24 Refs) (In GER)

58. LONG-TERM FOLLOW-UP OF PATIENTS WITH LEUKEMIA RECEIVING PLATELET TRANSFUSIONS: IDENTIFICATION OF A LARGE GROUP OF PATIENTS WHO DO NOT BECOME ALLOIMMUNIZED.

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Blood; 58(5):1007-1011 1981

Alloimmunization is the major complication of platelet transfusion therapy in patients with acute leukemia. To evaluate whether alloimmunization continues to be a long-term problem in patients surviving induction therapy, 114 patients with acute nonlymphocytic leukemia (ANLL) who survived more than 6 mo and who received multiple courses of chemotherapy and abundant platelet transfusions were studied. Clinical response to random donor platelets and lymphocytotoxic antibody (LCTAb) were measured pretreatment and serially throughout the study period. Fourteen patients (12%) were alloimmunized upon admission, 34 (30%) patients became alloimmunized during remission induction therapy, and 66 (58%) patients did not become alloimmunized during that period. Sixty-one of these 66 patients (92%) never became alloimmunized and responded to random donor platelets during their subsequent course despite the fact that they received multiple further platelet transfusions, whereas the alloimmunized patients tended to remain alloimmunized for their entire clinical course. There was no difference in age or sex between groups, and prognostic factors predicting alloimmunization could not be detected. In greater than 90% of patients not alloimmunized at admission, the presence or absence of LCTAb after induction predicts later alloantibody production. This information can be used to plan the type of platelet transfusions (HLA-matched or random donor) nee ded for subsequent maintenance and induction therapy. It may also help to identify a group of patients to whom more aggressive maintenance chemotherapy may be more safely administered. (Author abstract) (19 Refs)

59. COLLECTION AND CRYOPRESERVATION OF PERIPHERAL BLOOD PROGENITOR CELLS IN CHRONIC GRANULOCYTIC LEUKAEMIA - A COMPARISON OF TREATED AND UNTREATED PATIENTS.

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Pathology; 13(3):609-614 1981

Buffy coat cells were collected by leukapheresis from 14 patients with chronic granulocytic leukemia (CGL) and one patient with myelofibrosis, myeloid metaplasia. Six of the CGL patients had received busulfan at intervals varying between 401 and 38 days before leukapheresis. Significantly more CFUc's could be collected per leukapheresis in untreated patients and in those patients not treated within 105 days prior to leukapheresis. Survival of CFUc's following freezing was significantly less in the three most recently treated patients. These results suggest that in CGL patients recently treated with busulfan, both the number of CFUc's in the peripheral blood and the ability of these cells to survive the freeze thaw process are reduced. However, sufficient CFUc's could theoretically be collected, stored and recovered post-thaw from one leukapheresis to allow complete hematopoietic restoration in all but two patients. (Author abstract) (12 Refs)

60. LESSONS LEARNED FROM SURVEILLANCE CULTURES IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKEMIA. USEFULNESS FOR EPIDEMIOLOGIC, PREVENTIVE AND THERAPEUTIC RESEARCH.

Newman KA, Schimpff SC, Young VM, Wiernik PH
Baltimore Cancer Res. Program, NCI, Univ. Maryland Hosp., 22 South Greene St., Baltimore, MD, 21201
Nosocomial Infections, Proceedings of the 2nd International Conference on Nosocomial Infections held in Atlanta, 5-8 August, 1980. Center for Disease Control. Atlanta, GA. Dixon, R. E., ed. (New York, Yorke Medical Books), 326 pp., 1981.

Forty-eight patients with acute nonlymphocytic leukemia (ANLL) who were not given any specific prophylaxis and 97 patients with ANLL given oral nonabsorbable antibiotics and other prophylaxis had nasal, gingival, axillary, rectal, and urine specimen cultures taken on hospital admission and at least 2x/wk thereafter for varying periods. The baseline cultures indicated that patients with ANLL have a greater than expected colonization by gram-negative bacilli (GNB). Some of these bacilli were associated with subsequent bacteremia during periods of mucosal damage and granulocytopenia. New organisms (mostly GNB) were acquired at the rate of 0.5 organism/patient/wk in those patients given prophylaxis; the rate was lower than that in patients not given prophylaxis. The routine cultures indicated that it is possible to identif y subpopulations of patients at increased risk for acquisition of certain yeast infections. Routine use of surveillance cultures outside an epidemiology research setting is not recommended. (31 Refs)

61. PREVENTION OF INFECTION DURING INDUCTION THERAPY FOR ACUTE LEUKEMIA.

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Klin Wochenschr; 59(19):1075-1079 1981

Induction therapy for leukemia carries a risk of infection due to granulocytopenia. Prophylactic granulocyte transfusion has not been successful due to high cost and substantial risk to the patient. Gnotobiotic manipulation has not been successful. Total decontamination (TD)involves eradication of the microbial flora with antibiotics and maintenance of patient in strict reverse isolation. This method is not as successful in adults as in children, but reduces the frequency of infection. It carries the risk of more serious infection by pathogens in the absence of benign microflora. Selective decontamination (SD) involves elimination of facultative pathogens without affecting anaerobic flora by the use of drugs such as cortimoxazol. Treatments are most effective against gram-negative bacterial, but fungi are not as easily controlled. Gram-positive bacteria are largely unaffected by SD. Results of SD are comparable to those achieved by TD, but at lower cost and with less physical and psychological burden on the patient. (18 Refs) (In GER)

62. ISOLATION, NONADSORBABLE ANTIBIOTICS, AND INTRAVENOUS ADMINISTRATION OF GENTAMYCIN IN PROPHYLAXIS OF INFECTIOUS COMPLICATIONS IN LEUKEMIA PATIENTS UNDERGOING CYTOSTATIC CHEMOTHERAPY.

Baranov AE, Petrosian LN, Nadezhina NM, Shishkova TV, Nesterova VI, Selidovkin GD
Inst. Biophysics, Moscow, USSR
Ter Arkh; 53(9):45-50 1981

The efficacy of isolation of the patient, sterilization of intestinal microflora with the aid of the nonadsorbable antibiotics kanamycin, ristomycin, and nystatin, and iv administration of gentamycin was evaluated in 20 patients (10 men, 10 women; 16-55 yr old) who had acute leukemia or blast crisis of chronic myeloid leukemia and who were treated with rubomycin and cytosar. In the patients who had cytopenia (induced by the chemotherapeutic agents), isolation of the patient and treatment with antibiotics brought about 2-5-fold fewer infectious complications than in the corresponding controls not so treated. Severe infectious complications (sepsis, pneumonia, necrotic enteropathy) were 5-8x less frequent. (22 Refs) (In RUS)

63. PREVENTION OF INFECTION BY TRIMETHOPRIM-SULFAMETHOXAZOLE PLUS AMPHOTERICIN B IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKAEMIA.

Dekker AW, Rozenberg-Arska M, Sixma JJ, Verhoef J
Univ. Hosp. Utrecht, Catharijnesingel 101, 3511 GV Utrecht, The Netherlands
Ann Intern Med; 95(5):555-559 1981

Fifty-two patients with acute nonlymphocytic leukemia were studied during remission induction treatment in a randomized trial to ascertain the effect of prophylactic oral trimethoprim-sulfamethoxazole on infection and fever rate. A decrease in the total number of acquired infections was found (16 infections in the group given trimethoprim-sulfamethoxazole versus 31 in the control group, p less than 0.01). The number of patients without any infection in the trimethoprim-sulfamethoxazole group was 13 compared to only 3 in the control group (p less than 0.01). Patients in the trimethoprim-sulfamethoxazole group needed parenteral antibiotics during 33% of the days they were granulocytopenic compared to 61% of these days for patients in the control group. However, 6 of 9 bacteriologically documented infections in the trimethoprim-sulfamethoxazole group was caused by resistant microorganisms compared to 2 out of 20 in the control group. (Author abstract) (18 Refs)

64. DECREASED INCIDENCE OF NONSPECIFIC INTERSTITIAL PNEUMONITIS IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA TREATED PROPHYLACTICALLY WITH TRIMETHOPRIM-SULFAMETHOXAZOLE.

Morgan E
Children's Memorial Hosp., 2300 Children's Plaza, Chicago, IL, 60614
J Pediatr; 99(5):807-810 1981

Interstitial Pneumonitis is a significant cause of morbidity and mortality occurring during remission in children with acute leukemia. Beginning in May, 1978, we noted an outbreak of Pneumocystis carinii pneumonia children at our institution with ALL. Therefore, in January, 1979, we began the routine use of prophylactic trimethoprim-sulfamethoxazole therapy in all newly diagnosed patients with ALL. Subsequently, the incidence of PCP in these patients, as expected, dropped to nearly zero. Surprisingly, however, we noted a concomitant decrease in the incidence of nonspecific interstitial pneumonitis in patients with ALL. The results of a retrospective analysis of the incidence of all types of IP in patients with ALL are presented in this report. (Author abstract) (10 Refs)

65. PREVENTION OF INFECTION AND BLEEDING IN LEUKEMIC PATIENTS RECEIVING INTENSIVE REMISSION MAINTENANCE THERAPY.

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Med Pediatr Oncol; 9(5):511-521 1981

Leukemic patients were treated with intensive chemotherapy to reduce the number of leukemic cells remaining after complete remission was induced. This therapy resulted in periods of severe granulocytopenia and thrombocytopenia. Considering 13 patients who did not receive antibacterial prophylaxis, documented infection was quite common including four episodes of bacteremia and three urinary tract infections. By contrast, patients who received co-trimoxazole as antibacterial prophylaxis experienced on e half as many febrile episodes and no serious infections. Prophylactic co-trimoxazole is beneficial for patients with marrow remission in this study. Similar benefit in patients with leukemic marrows remains to be established. All patients received prophylactic platelet transfusions three times a wk when their platelet counts were less than 20,000/ul. There were no episodes of bleeding other than petechiae. (Author abstract) (6 Refs)

66. APPLICATION OF A LIVE VARICELLA VACCINE IN CHILDREN WITH ACUTE LEUKEMIA OR NEPHROTIC SYNDROME.

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Dept. Pediatrics, Taipei Medical Coll. Hosp., Taipei, Taiwan, Republic of China

J Formosan Med Assoc; 80(7):683-690 1981

Eight children with acute leukemia (AL: 6 acute lymphoblastic and 2 acute myeloblastic) in remission and nine with nephrotic syndrome (NS) were treated with live varicella vaccine. All 17 children were skin test negative for varicella. Seroconversions were demonstrated in all of the six of the AL children who had no detectable antibodies prior to vaccination. Among three AL patients who had a follow-up skin tests 10 mo after vaccination, none became positive. No adverse reactions to the vaccine were observed in the AL children during the 1-yr follow-up. One child, who developed skin rashes on two separate occasions and a fever 18 days after vaccination, was found to have been exposed to varicella near the time of treatment. All of the five NS children who had checked delayed hypersensitivity skin tests showed at least a positive reaction to the antigens tested. Among the nine NS children vaccinated, eight showed serological response 4 wk after vaccination. No adverse effects were observed. One patient developed clinical features compatible with typical varicella 9 mo after vaccination following exposure to a child with varicella. Of 5/9 NS patients in whom follow-up varicella skin tests were performed, only one was positive. The protection provided immunocompromised patients by live varicella vaccine is discussed. (16 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

67. DOWN SYNDROME AND ACUTE LEUKAEMIA: INCREASED RISK MAY BE DUE TO TRISOMY 21.

Rowley JD

Section Hematology/Oncology, Dept. Medicine, Univ. Chicago, Chicago, IL, 60637

Lancet; 2(8254):1020-1022 1981

Individuals with Down syndrome (DS), especially children, have an increased incidence of acute leukemia. It is suggested that this increased risk is specifically associated with the presence of an extra chromosome 21 (+21) as a constitutional abnormality. Data available from surveys of non-DS patients with acute lymphocytic leukemia (ALL) and acute non-lymphocytic leukemia (ANLL) indicate that a +21 is the most common change in leukemic cells in ALL, especially in children, and that it is one of the more common changes in ANLL. In neonatal patients with mosaicism for normal cells and +21 cells who have a transient leukemoid reaction, the blast cells involve the +21 clone; spontaneous disappearance of the leukemoid reaction parallels a decrease in +21 cells in the bone marrow. Thus, the increased risk of acute leukemia in patients with DS who have a +21 is directly related to the presence, in all cells of these individuals, of the same chromosome change that is commonly seen in the leukemic cells of children with ALL, the type of leukemia most commonly seen in DS children. This observation is analogous to that for two other constitutional chromosome abnormalities that are associated with an increased risk of a malignant tumor. A deletion of chromosome 13, including band 13q14 is associated with retinoblastoma, and a deletion of chromosome 11, including band 11p13 is associated with aniridia/Wilms tumor syndrome. The nature of the genes affected by these various chromosome aberrations is unknown. (Author abstract) (20 Refs)

68. FAMILIAL LEUKEMIA: PH1 POSITIVE ACUTE LYMPHOID LEUKEMIA OF A MOTHER AND HER INFANT.

Olah E, Stenszky V, Kiss A, Kovacs I, Balogh E, Karmazsin L

Dept. Pediatrics, Univ. Medical Sch., POB 32, H-4012, Debrecen, Hungary

Blut; 43(4):265-272 1981

Acute lymphoid leukemia (ALL) was diagnosed in a mother and her 9-mo-old infant. The mother's symptoms (paleness, weakness, anemia) began during the second half of pregnancy. The mother achieved a short remission but died 15 mo after diagnosis. The infant remained in remission 23 mo after diagnosis. Both leukemia process were of 'O' cell character (mother: RBC-rosette forming cells:37%, cells with surface immunoglobulins: 2%, and non-T non-B-cells: 61%; infant: 18%, 10%, and 72%). The infant was human leukocyte antigen-identical with one of her healthy brothers, and haplo-identical with the other. Both ALL were Philadelphia chromosome (Ph1)-positive. During remission, Ph1 disappeared temporarily. In mo 17 of disease, the infant's bone marrow showed a normal karyotype. (35 Refs)

69. ACUTE LEUKAEMIA AND THE SAME CHROMOSOME ABNORMALITY IN MONOZYGOTIC TWINS.

Hartley SE, Sainsbury C
MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh EH4 2XU, Scotland
Hum Genet; 58(4):408-410 1981

Two monozygous twins with a 47,XX,+19 karyotype were diagnosed as having acute lymphoblastic leukemia at the age of 17 mo and 36 mo, respectively. Both patients presented with a history of pallor and bruising. Aggressive chemotherapy failed to produce remission in twin I and was abandoned and exchanged for supportive prednisolone treatment in twin II. Twin II also possessed a few cells with 46,XX,-11,-Abn karyotype. These cases provide evidence for in utero transformation. (15 Refs)

SELECTED PRE-CLINICAL STUDIES

70. LEUKEMIC CELL TARGETING AND THERAPY BY MONOCLONAL ANTIBODY IN A MOUSE MODEL SYSTEM.

Scheinberg DA, Strand M
(c/o Strand) Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Cancer Res; 42(1):44-49 1982

A monoclonal antibody prepared against the Rauscher virus envelope glycoprotein with a mol wt of 70,000 targeted to neoplastic cells and cured the Rauscher leukemia virus-induced erythroleukemia in BALB/c mice. This antibody, 103A, specifically reacted with the Rauscher and Friend erythroleukemia viruses and erythroleukemic cells but did not react with other murine ecotropic or xenotropic viruses or feline leukemia virus or with normal spleen cells, thymocytes, or fibroblasts, as measured by radioimmunoassays. P3, a control antibody of the same Ig G1 subclass, did not bind to any of these cells or viruses. This specificity was maintained in vivo. 125I-Labeled 103A injected into mice targeted to leukemic spleen cells but not to normal cells. Mean uptake ratios of binding to leukemic over normal spleen cells ranged from greater than 70 at 7 hr after injection to less than 10 at 40 hr later. The control antibody showed no binding in vivo. A single small dose of 103A was able to cure leukemic mice as assayed by spleen focus formation on Day 8 or splenomegaly on Day 20. The 50% effective dose was 1.5 ug when injected 72 hr after onset of leukemia. The therapeutic potencies of drugs, toxins, and cytotoxic radioisotopes conjugated to antibodies can be quantitatively compared using the established dose-response curve. Such quantitative comparisons showed that 131-labeled 103A Ig G was no more potent than unlabeled 103A Ig G in this system. (Author abstract) (39 Refs)

71. THE MECHANISM OF INHIBITION OF HAEMOPOESIS IN ACUTE LEUKEMIA.

van Bekkum DW, Prins ME, Hagenbeek A, Cronkite EP, Brecher G, Lajtha L, Boggs D, Bessis M, McCullogh EA, Fauser AA, Bernard J
Radiobiological Inst. TNO, P. O. Box 5815, 2280 HV Rijswijk, The Netherlands
Blood Cells; 7(1):91-103 1981

Studies with a rat model for acute myeloblastic leukemia (AML), the the transplantable Brown Norway myeloid leukemia (BNML), revealed a nearly complete suppression of hemopoiesis in an early stage of the disease that was attributable to the disappearance of hemopoietic stem cells (HSC) from the bone marrow; the few HSC left in the bone marrow in the terminal stage of the disease were largely out of cycle, unlike HSC in normal rat bone marrow. The disappearance of HSC from the bone marrow in BNML was only partly compensated for by an increased number of HSC in the spleen. BNML cells behave differently than cells of acute lymphocytic leukemia (ALL) when injected into normal rats: while both types of cells home to the subendosteal region of the femoral bone marrow, ALL cells then become randomly distributed over the whole m arrow space but BNML cells remain localized in the subendosteal region. These results support the hypothesis that the depression of normal hemopoiesis in AML is caused by a specific localization and proliferation of AML cells in the subendosteal area, which, in normal bone marrow has a higher percentage of proliferating blast cells than the central area of the marrow and provides the optimal microenvironment for HSC self-replication. It is further suggested that the more severe depression of normal hemopoiesis in ALL that occurs in the later stage of the disease is due to the random replacement of HSC by non-specific overgrowth. (27 Refs)

REVIEWS

72. HAIRY-CELL LEUKEMIA (LEUKEMIC RETICULOENDOTHELIOSIS).

Rupniewska ZM
Klinika Hematologii, Instytut Chorob Wewnetrznych AM, ul. Jaczewskiego 8, 20-950 Lublin, Poland
Przegl Lek; 38(7):555-560 1981

Studies on hairy-cell leukemia (HCL) are reviewed. HCL occurs usually beyond the age of 50 yr, and is 4x more frequent among men than among women. Splenomegaly, associated with hypersplenism, is encountered in 93% of all cases, hepatomegaly in 43%, and lymph node enlargement in 23%. Tendency to fibrosis in affected lymph nodes, lymphoidal myelofibrosis in bone marrow, cytopenia, hemorrhage, anemia, and recurrent infections are common features of HCL. The serum immunoglobin levels are within normal limits. The mean survival is 5-6 yr. Splenectomy is the treatment of choice. (91 Refs) (In POL)

73. TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA OF CHILDHOOD. PRESENT INQUIRIES.

Ortega JJ
Aribau, 200, primero, cuarta, Barcelona-6, Spain
Sangre (Barc); 26(5B):824-844 1981

The results in treatment of, and the inquiries posed by childhood acute lymphoblastic leukemia (ALL) are reviewed. With the therapy currently used 95% of the patients attain initial remission; of them, 60% maintained it for the 36 mo of treatment, while relapses appeared in 20-25% of cases after cessation of all therapy. Curation can be achieved in about 40% of the adequately treated children. The majority of patients relapsing during treatment had one or more unfavorable factors (high blast count, age under 1 yr or beyond 12, T-cell markers, mediastinal mass, or CNS involvement), so the present trend is to disclose the high risk patient groups in order to try new therapeutical approaches. The management of the meningeal

relapses has not been satisfactory; intrathecal chemotherapy followed by craniospinal irradiation and simultaneous intensification of systemic chemotherapy appears to bring certain advance. There is higher incidence of initial testicular relapses as shown by different series, along with a number of leukemic infiltrates in the testicular biopsies performed after 3 yr of complete remission and the higher incidence of relapses in males after cessation of therapy represents an interesting problem. The duration of tr eatment, 30-36 mo, appears as adequate for the majority of girls (15% relapses) but it is not enough for the boys. Of special importance among the late toxic effects are the neurotoxicity of CNS treatments and their effect on intellectual functions, the gonadal toxicity and its possible effects on the offspring, and the development of second neoplasms. Attention must be paid in a few yr to the presently experimental treatments, including the assay of new drugs, the results of improved bone-marrow transplantation techniques for relapse and second remission cases, and the advances in immunotherapy, especially with monovalent antibodies. (109 Refs) (In SPA)

74. CHRONIC MONOCYTIC LEUKEMIA IN ADULTS.

Bearman RM, Kjeldsberg CR, Pangalis GA, Rappaport H
(c/o Rappaport), City of Hope Natl. Medical Center, 1500 East Duarte Road, Duarte, CA, 91010
Cancer; 48(10):2239-2255 1981

Clinical, hematologic, and histologic material from 5 patients with chronic monocytic leukemia is analyzed, and the literature is reviewed on 28 patients either reported as having this disease or referenced as such in subsequent publications. Patients with chronic monocytic leukemia have a characteristic clinical course. All have splenomegaly of uncertain etiology, and initial hematologic evaluation usually shows anemia with normal WBC and differential counts. One of the authors' patients had slight monocytosis at presentation. In the four patients for whom presplenectomy bone marrow smears were available for review, there was no detectable increase in the number of monocytes. The patients developed monocytosis, usually with accompanying leukocytosis, at intervals ranging from 3.5 to 24 mo after splenectomy. In all patients, there was a corresponding increase in the numbers of mature monocytes in the bone marrow. Survival times for the detection of monocytosis ranged from 5 to 8 mo. Of the 28 cases reported in the literature, only two were considered by the authors of this study to have the characteristics of chronic monocytic leukemia, and of these, only one had features identical to those reported in the present series. The remainder represent a variety of hematologic disorders including chronic myelomonocytic leukemia, acute leukemia, histiomonocytic proliferations that cannot be subclassified, and cases in which the data are insufficient for analysis. The differential diagnosis includes chronic myelomonocytic leukemia, chronic malignant histiocytosis, and hairy cell leukemia. In chronic monocytic leukemia, in contrast to hairy cell leukemia, splenectomy does not appear to be beneficial. Although chronic monocytic leukemia is an extremely rare disease, it is a distinct hematologic entity that appears to have a characteristic clinical course. (Author abstract) (55 Refs)

75. BIOLOGICAL AND IMMUNOLOGICAL MARKERS IN ACUTE LEUKAEMIA.

Lopez Borrasca A, Gonzalez M, Hernandez F, Ledesma M, Corrales A, San Miguel J
Servicio de Hematologia, Hospital Clinico Universitario, Salamanca, Spain
Sangre (Barc); 26(5B):756-782 1981

The authors present a review of the value of immunologic and enzymatic markers in the diagnosis of the different types of acute leukemia (AL). The addition of such markers to the classical morphologic and cytochemical criteria is advisable since they provide the means for AL subclassifications to be used with therapeutical purposes. The markers are divided into (a) surface receptors: sIg, C receptors, Fc receptors, non-immunologic spontaneous rosettes with different red-cells and viral receptors; and (b) surface antigens, including T-lymphocytes surface antigen, B-lymphocyte antigens, common ALL antigen and myeloid cells antigen. Their significance is detailed, along with other data including their study techniques, the levels in different leukemic populations, and the value of such markers in the immunologic differential-diagnosis of the leukemias. The enzymatic markers, terminal deoxynucleotidyl transferase, adenosine-deaminase, nucleoside-phosphorylase, 5'-nucleotidase, and hexosaminidase (N-acetyl-B-glucosaminidase) are considered. Following the pattern referred to, an analysis is made of the significance of, and study methods for, these sort of markers, along with their clinical interest and the correlation they may show with the immunologic markers mentioned above. Classifications are suggested based on the phenotypes of the leukemic cells. These phenotypes correspond to T-cell, B-cell, and non-T, non-B lymphoblastic leukemias, as well as to the blastic crises of chronic granulocytic leukemia; and the phenotypes of the acute myeloblastic leukemias are also considered. The application of the methodology commented in this paper has provided a new variant, the pre-B acute leukemia, which is characterized by possessing cIgM. (173 Refs) (In SPA)

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DIAGNOSIS

1. DIAGNOSTIC PROBLEMS IN THE CYTOLOGIC EVALUATION OF CEREBROSPINAL FLUID FOR LYMPHOMA AND LEUKEMIA.

Borowitz M, Bigner SH, Johnston WW
Dept. Pathology, Duke Univ. Medical Center, Box 3712, Durham, NC, 27710
Acta Cytol (Baltimore); 25(6):665-674 1981

We reviewed 72 cerebrospinal fluid (CSF) specimens with abnormal hematopoietic cells and the clinical records of the 45 patients from whom they were obtained. Of the 72 specimens, 34 were originally diagnosed as positive for lymphoma or leukemia and the remaining 38 as 'atypical cells present.' Based on

HE20.3173/2:

follow-up information of the patients, only 3 'atypical' specimens were from patients with CSF leukemia, but 10 of the positive diagnoses were incorrect. Cases of acute lymphoblastic leukemia (ALL) produced cells with a characteristic morphology. Cells of five of the six false-positive specimens in this disorder were, in retrospect, markedly different from typical blasts. In contrast, two false-positive reactive cases from patients with no established malignancy had an infiltrate whose morphology was indistinguishable from that of many cases of diffuse histiocytic lymphoma (DHL). There were no cases of chronic lymphocytic leukemia (CLL) or nodular poorly differentiated lymphocytic lymphoma involving CSF, but two patients with CLL and infectious meningitis had false-positive cytologies. We conclude that in evaluating CSF specimens for lymphoma or leukemia, knowledge of the morphology and behavior of a patient's particular tumor can minimize incorrect diagnostic interpretations. (Author abstract) (16 Refs)

2. SPLENIC ALTERATIONS IN HAIRY CELL LEUKEMIA I. A LIGHT MICROSCOPIC AND HISTOCHEMICAL STUDY (MEETING ABSTRACT).

Pilon V, Davey FR, Gordon GB
Division of Clinical Pathology, State University of New York Upstate Medical Center, Syracuse, NY, 13210
Am J Clin Pathol; 76(3):354 1981

Spleens from 12 patients with hairy cell leukemia (HCL) were studied for the presence of morphologic and histochemical alterations. Hairy cells were present in great numbers within the splenic sinuses and cords but few were observed in the atrophic white pulp. Hairy cells adhered to splenic endothelial cells, other hairy cells and RBC. Large clumps of hairy cells filled and occluded splenic sinuses. Dilated sinuses, pseudosinuses, and blood lakes were present. Normal splenic sinuses were lined by endothelial cells encircled by ring fibers. Pseudosinuses were lined by hairy cells and a few attenuated endothelial cells. Ring fibers around pseudosinuses were fragmented and reduced in amount. Blood lakes were lined by hairy cells without the presence of either endothelial cells or ring fibers. Reticular fibers appeared increased around some pseudosinuses. However, reticular fibers were decreased in areas surrounding the blood lakes and in most distended splenic cords. Subendothelial lymphatics of trabecular veins were infiltrated by hairy cells, sometimes resulting in a compromise of the lumen. Formation of pseudosinuses and blood lakes probably result from obstruction of venous blood flow and from injury or death of sinus endothelial cells. (no Refs)

3. PROGNOSTIC VALUE OF SERIAL MEASUREMENTS OF LEUKOCYTE THYMIDINE UPTAKE IN WELL-CONTROLLED CHRONIC MYELOCYTIC LEUKEMIA.

Gomez GA, Herrmann R, Sokal JE
Dept. Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Leuk Res; 5(6):497-503 1981

Serial simultaneous determinations of uptakes of 3H-thymidine (3H-Tdr) by blood and marrow WBC in 29 patients (10 males, 19 females; 12-71 yr old) with well-controlled, Philadelphia chromosome-positive chronic myelocytic leukemia (CML) were examined for ability to provide early warning of disease progression from chronic to terminal stage. The 3H-TdR uptake values varied considerably from patient to patient (median values 0.9-18 disintegrations/min/10(3) WBC); these values were not, however, significantly different from those of controls. Also, the 3H-TdR uptake was not affected significantly by changes in the chemotherapy agents administered. Eleven patients (Group I) had a greater than four-fold increase in blood 3H-TdR between sequential determinations. Ten of the Group I patients entered the terminal phase of CML 2-6 mo after the increase in 3H-TdR uptake; 9/10 patients died 7-34 mo (median 10 mo) after the increase. One of the 18 patients (Group II) whose 3H-TdR did not increase died of ulcerative colitis, with CML under good control; 5 of the remaining 17 patients entered terminal phases 5, 6, 7, 8, and 12 mo after the last evaluable determination. The proportion of patients exhibiting disease progression was significantly less in Group II (28% within 1 yr; 11% within 6 mo) than in Group I. The marrow 3H-TdR did not show any consistent trend in either group and had no prognostic importance. Hematologic findings in blood and marrow at the time of 3H-TdR increase and at the time of the last previous evaluable study are presented. Chromosome analysis of the CML patients is described. The results indicated that periodic measurement of 3H-TdR uptake by circulating WBC may be useful for providing early warning of disease progression in the follow-up of patients with well-controlled CML. (15 Refs)

4. CLINICAL SIGNIFICANCE OF IDENTIFICATIONS OF TDT-POSITIVE CELLS BY INDIRECT IMMUNOFLUORESCENCE ASSAY IN BONE MARROW CELLS FROM PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA.

Hida K, Sakamoto S, Kano Y, Tsuboyama A, Suda K, Takaku F
First Dept. Internal Medicine, Jichi Medical Sch., Tochigi, Japan
Nippon Ketsueki Gakkai Zasshi; 44(6):1139-1146 1981

TdT-positive cells in bone marrow mononuclear (bmm) cells from 5 normal adult subjects, 9 patients with CML in chronic phase and 16 patients with CML in blast crisis were examined by indirect immunofluorescence technique. TdT-positive cells (0.1 to approx 0.6%, mean 0.3%) were found in the bmm cells obtained from five normal adult subjects. No TdT-positive cells were identified in more than one thousand bmm cells from nine patients with CML in chronic phase. On the other hand, 4 to approx 90% of TdT-positive cells were found in the bmm cells from 8 out of 16 patients with CML in blast crisis. Blast cells from eight TdT-negative patients with CML in blast crisis were classified morphologically as myeloid blasts on the basis of Wright-Giemsa stain. Blast cells from six of eight TdT-positive patients were classified morphologically as lymphoid blasts. Blast cells of the other two TdT-positive patients were considered to be a mixture of lymphoid and myeloid blasts morphologically, and in one, the blast cells consisted of both TdT-positive and TdT-negative blast cells. As no TdT-positive cells were found in bone marrow cells from patients with CML in chronic phase, it was considered that assay for TdT-positive cells by immunofluorescence technique might be useful for the earlier detection of TdT-positive blastic transformation of CML. It was also shown that serial observation of bone marrow cells by the indirect immunofluorescence assay for TdT were useful for the assessment of the efficacy of V-P therapy during the course of blast crisis of CML. (22 Refs) (In JPN)

5. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN ADULT LYMPHOBLASTIC LEUKEMIA: RELATIONSHIP WITH BLAST CELL COUNT.

Baccarani M, Marini M, Bagnara G, Gobbi M, Saviotti F, Brunelli M, Tura S
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Haematologica (Pavia); 66(5):579-587 1981

The relationship of blast cell count to terminal deoxynucleotidyl transferase (TDT) levels were studied. Biochemical assays were carried out on the peripheral blood cells of 27 adult patients with acute lymphoblastic leukemia (ALL) TDT activity was positive in 18/19 patients with blast cell counts greater than 0.5 x 10(3)/ul. All patients who were positive when assayed for RBC rosette formation and for surface immunoglobulins were TDT positive. A number of patients with TDT positive blast cells were studied during induction therapy or at early relapse when their blast cell counts were lower than 0.5 x 10(3)/ul. In 11/20 assays, TDT was detectable in spite of the very low blast cell number. In patients presenting with 'oligoblastic' leukemia (mean blast cell count 0.15 x 10(3)/ul), the TDT assay was always negative. The comparison of results suggested that in the oligoblastic patients, TDT negativity was not merely due to the paucity of blast cells in the sample studied, but reflected a true absence or a very low level of enzyme activity. (13 Refs)

6. CLINICAL SIGNIFICANCE OF SERUM LYSOZYME IN LEUKEMIA.

Nishikori M, Emi Y, Yoshida Y, Murachi T
Central Clinical Lab., Kyoto Univ. Hosp., Kyoto, Japan
Naika Hokan; 28(4):79-84 1981

Serum lysozyme levels were measured in 64 patients with various types of leukemia and were compared to those in 15 healthy subjects. The patients included 15 with acute myelogenous leukemia, 2 with premyelocytic leukemia, 17 with monocytic leukemia, 2 with erythroleukemia, 19 with chronic myelogenous leukemia, 4 with acute lymphogenous leukemia, 1 with chronic lymphogenous leukemia, 1 with hairy cell leukemia, 1 with sideroblastic anemia, and 1 with myelofibrosis. Normal levels of serum lysozyme were 8.0 +-4.7 ug/ml. Abnormally high levels (greater than 20 ug/ml) of serum lysozyme were observed in 1/16 patients with acute myelogenous leukemia, 12/17 with monocytic leukemia, and 9/19 with chronic myelogenous leukemia. High levels of serum lysozyme were observed in 67% of the cases of chronic myelogenous leukemia in the chronic stage, but 6/7 patients in the acute transformation stage had normal levels of lysozyme. Pretreatment levels of serum lysozyme were not related to prognosis of the patients with acute leukemia. On the other hand, because serum lysozyme was thought to be derived primarily from the in vivo lysis of mature granulocytes and monocytes, measurements of serum lysozyme activity were thought to be useful in evaluating antileukemia therapy and subsequent exacerbation of the disease. (18 Refs) (In JPN)

7. BIOCHEMICAL ACTIVITIES OF LYSOSOMAL ACID HYDROLASES IN LEUKEMIC CELLS.

Tanaka T, Kobayashi M, Saito O, Kamada N, Kuramoto A, Usui T
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Clin Chim Acta; 117(2):121-131 1981

The biochemical activities of eight lysosomal hydrolases were determined in various types of leukemic cells with 4-methylumbelliferyl compounds. Among the hydrolases, characteristic alterations were found with alpha-mannosidase (a-MAN), beta-galactosidase (b-GAL), and N-acetyl-beta-glucosaminidase (NABG) in cells from 48 patients with different types of leukemia. a-MAN was markedly higher in various myelogenous leukemia (acute myelogenous leukemia, acute monocytic leukemia [AMoL], acute myelomonocytic leukemia [AMMoL], chronic myelogenous leukemia [CML], and chronic myelomonocytic leukemia [CMMoL]) than in lymphogenous leukemias (acute lymphogenous leukemia, T-cell leukemia, hairy cell leukemia, and chronic lymphogenous leukemia) without exception. b-GAL activity also showed differences between lymphogenous and myelo(mono)genous leukemia with the exception of T-cell leukemia. NABG activity in myelo(mono)genous leukemic cells was above the range of normal granulocytes. The changes in the enzyme levels were consistent. The lymphocytic or myelocytic nature of three cases of acute undifferentiated leukemia could be determined by these enzyme studies. The enzymatic abnormalities were also found in morphologically mature neutrophils from patients with not only chronic types (CML, CMMoL), but also in acute types (AMoL, AMMoL) of leukemia, and were similar to the enzymic abnormalities of the respective leukemic cells. Also described are the activities of beta-glucuronidase, alpha-galactosidase, alpha-fucosidase, acid phosphatase, and aryl sulfatase. Analysis of lysosomal enzymes may be valuable in the differentiation of leukemias. (24 Refs)

8. HIGH LEVELS OF 5'-NUCLEOTIDASE ACTIVITY IN BLASTIC CHRONIC MYELOGENOUS LEUKEMIA WITH COMMON ALL-ANTIGEN.

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Leuk Res; 5(6):505-510 1981

Levels of 5'nucleotidase (5'-N) on surfaces of leukemia cells were determined for 44 patients in lymphoid blast crisis (LY-BC) of chronic myelogenous leukemia (CML) with or without common acute lymphoblastic leukemia (cALL) antigen (cALLA) and for 52 patients with acute myeloblastic (AML) or acute lymphoblastic (ALL) leukemia. The 5'-N activities of mononuclear cell preparations from 50 healthy blood donors ranged from 1.2 to 14.5 nanomoles AMP hydrolyzed/hr/10(6) cells; this activity was mainly due to T and B lymphocytes. In 12 cases of cALL, blast cells derived from blood and bone marrow of the same patient were compared; no difference in immunological phenotype expression was noted, and the 5'-N activity was the same in both cell sources. Cells from the AML patients, diagnosed mainly on the basis of hematological criteria, were cALLA-negative. Diagnosis of the cALL patients was based on the absence of B or T markers and the expression of cALLA. The difference in 5'-N activities of AML and cALL cells and the difference in 5'-N activities of myeloid blast crisis (MY-BC) and LY-BC cells were both statistically significant. A wide overlap in 5'-N activities for AML and cALL limits the usefulness of the 5'-N determination. No overlap of 5'-N activity was observed, however, for the LY-BC and MY-BC cells. The LY-BC cells of CML characterized by cALLA had high 5'-N levels, while cALLA-negative blast crisis was correlated with a decrease in 5'-N activity. The results indicated that 5'-N affords an additional, easily-testable biochemical marker that may have diagnostic and prognostic value in blastic CML. (31 Refs)

9. ADENOSINE DEAMINASE AND ECTO-5'-NUCLEOTIDASE ACTIVITIES IN VARIOUS LEUKEMIAS WITH SPECIAL REFERENCE TO BLAST CRISIS: SIGNIFICANCE OF ECTO-5'-NUCLEOTIDASE IN LYMPHOID BLAST CRISIS OF CHRONIC MYELOID LEUKEMIA.

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Blood; 58(6):1107-1111 1981

Adenosine deaminase (ADA) and ecto-5'-nucleotidase (5'-N) activities were examined in peripheral leukocytes from patients with leukemias, including nine patients with chronic myeloid leukemia (CML) in blast crisis. Four of nine cases of CML in blast crisis were myeloid and the remaining lymphoid morphologically. The diagnosis of CML in lymphoid blast crisis was further contributed by the measurement of terminal deoxynucleotidyl transferase (TdT) activity. In all four cases of lymphoid blast crisis and one of myeloid blast crisis, leukemia cells had high 5'-N activity, while there was little or no detectable activity in those from four cases of myeloid blast crisis and all of CML in chronic phase. ADA activity was high in seven of nine patients with blast crisis. Taken together, leukemia cells from two cases of lymphoid blast crisis had high ADA and 5'-N activities comparable to those in acute lymphocytic leukemia (ALL) cells. In contrast, the enzyme activities of leukemia cells from all but one patient in myeloid blast crisis were in a range similar to acute myeloid leukemia cells. The implications of these findings are as follows: (1) 5'-N may be used as a new biochemical marker of CML in lymphoid blast crisis. (2) Some lymphoid cells of CML in blast crisis have high ADA, 5'-N, and TdT activities and thus are very similar to ALL cells. (Author abstract) (38 Refs)

10. IN VIVO AND IN VITRO ACTIVITY OF NEUTROPHIL ALKALINE PHOSPHATASE IN ACUTE MYELOCYTE LEUKEMIA WITH 8;21 TRANSLOCATION.

Kamada N, Dohy H, Okada K, Oguma N, Kuramoto A, Tanaka K, Uchino H
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Blood; 58(6):1213-1217 1981

Cytogenetic studies were made on 160 patients with acute nonlymphocytic leukemia (ANLL) between 1963 and 1979, of whom 115 had acute myelocytic leukemia with 67 patients showing aneuploidy (58.3%). Among these, 24 patients were found to have similar chromosome alterations that appeared to involve specifically chromosomes 8 and 21. Banding studies on at least seven of these patients confirmed the presence of a translocation between these two chromosomes. Of 160 ANLL patients, 142 were scored for neutrophil alkaline phosphatase (neutrophil AP) at the time of diagnosis. Fifty-nine patients showed a low neutrophil AP score, 42 a normal value, and 41 a high value. All patients with 8;21 (or C/G) translocation had a low neutrophil AP score and leukemic cells with maturation (M2 of FAB classification) in the bone marrow. In vitro liquid culture for 2 wk of 8;21 translocated leukemic cells revealed no increase of neutrophil AP activity nor increase of mature granulocytes, whereas 9;22 translocated chronic myelocytic leukemia cells with a low neutrophil AP score did so. Neutrophil AP score at the time of diagnosis in acute myelocytic leukemia is very useful for detecting 8;21 translocation AML and for studying the pathophysiology and genetic alterations of the characteristic subgroup of AML with 8;21 translocation. (Author abstract) (23 Refs)

11. URINARY NEOPTERINE AS MARKER FOR HAEMATOLOGICAL NEOPLASIAS.

Hausen A, Fuchs D, Grunewald K, Huber H, Konig K, Wachter H (c/o Wachter) Inst. Medical Chemistry and Biochemistry, Univ. Innsbruck, Fritz-Pregl-Strasse 3, A-6020 Innsbruck, Austria
Clin Chim Acta; 117(3):297-305 1981

Urinary noepterine levels (UNL) were studied in 79 normal subjects and in 112 pa tients with hematological neoplasias; chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia, Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL). Seventy nine of the patients with active disease were divided into two groups: first group (38 patients, 643.9 +-371 millimole neopterine/mole creatinine) was given chemotherapy and/or radiation therapy, and a second group (41 patients, 521.8 +-305 millimole neopterine/mole creatinine) with no treatment. Both groups showed higher neopterine levels than those of healthy individuals. Five patients who had undergone laparotomy were studied for 12 days to determine if UNL were affected by benign cell renewal. The highest UNL did not exeed the normal range. No significant difference was found between the mean UNL of 33 patients with NHL or 23 patients with HL in remission and the healthy group. The mean UNL correlated well with the tumor stage in 23 patients with CLL and in 23 with NHL. Patients without hepatosplenomegaly who had chronic leukemia excreted significantly more neopterine than healthy individuals. Patients with hepatosplenomegaly had significantly higher UNL than the patients without hepatosplenomegaly. Seventy-two of 79 patients with active disease had elevated UNL, and only 5/33 patients with disease in remission had elevated UNL. UNL can be of value for following the progression of hematological neoplasias. (16 Refs)

12. BIOCHEMICAL MARKERS AS INDICATORS OF PROGNOSIS IN ACUTE NONLYMPHOCYTIC LEUKEMIA (ANLL).

Skoog L, Nordenskjold B, Ost A, Andersson B, Hast R, Giannoulis N, Reitzenstein P
Dept. Pathology, Karolinska Hosp., Stockholm, Sweden
Adv Enzyme Regul; 19:287-293 1981

Twenty-five cases of ANLL were analyzed with respect to content of TdT, glucocorticoid receptor, adenosine deaminase and 5'-nucleotidase. We found that high levels of either TdT or the glucocorticoid receptor were positively correlated to both remission frequency and survival time. Thus, these two biochemical parameters contribute new valuable prognostic information in ANLL. We were unable to identify 5'-nucleotidase and adenosine deaminase as prognostic indicators in ANLL. (Author abstract) (10 Refs)

13. CHRONIC LYMPHOPROLIFERATIVE DISORDER RESEMBLING HAIRY-CELL LEUKEMIA.

Fohlmeister I, Schaefer HE, Modder B, Hellriegel KP, Fischer R
Pathologisches Institut der Universitat Koln, Joseph-Stelzmann-Strasse 9, D-5000 Koln 41, W. Germany
Blut; 42(6):367-377 1981

Seven cases of chronic lymphoproliferative disease resembling hairy-cell leukemia (HZL) are reported. Clinical findings included splenomegaly, discrete or no lymph node enlargement, and varying degrees of cytopenia. These symptoms, together with the demonstration of lymphoid cells with tartrate-resistant acid phosphatase (TSP) and hairy cell processes, suggested HZL. The hairy cells (HZ) were distinct from true HZ in possessing more fringe-like processes, basophilic cytoplasm,

and, in many cells, a strong granular beta-glucuronidase (b-GU) reaction. The TSP reaction was granular, rather than diffuse as in true HZ. Nonfibrotic nodular bone marrow infiltration suggested chronic lymphocytic leukemia (CLL), while nodular infiltration of the white pulp of the spleen suggested leukemic immunocytoma. Positive tartrate-sensitive acid phosphate and b-GU reactions differed from usual CLL characteristics. The cases reported are apparently an intermediate form of disease, requiring therapy distinct from those for CLL and HZL. (11 Refs) (In GER)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

14. PATHOLOGY OF T-PRECURSOR CELLS ACUTE LYMPHOBLASTIC LEUKEMIA - WITH SPECIAL REFERENCE TO SURFACE MARKERS.

Kawashima K, Kato Y, Ogura M, Suzuki H, Watanabe E, Takamatsu J, Minami S, Isobe K, Nagura E, Yamada K, Iwamura H, Yamamura M, Yokomaku S
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Rinsho Ketsueki; 22(7):1102-1108 1981

Characteristics of cell-surface markers on leukemia cells were determined in six patients (5 men, 1 woman; 6-28 yr old) with T-precursor cell acute lymphoblastic leukemia (ALL). The patients were administered various regimens of chemotherapy that included the following drugs: daunomycin, vincristine, prednisolone, endoxan, 6-mercaptopurine, cyclophosphamide, and procarbazine. Complete remission was induced in a short time in 5/6 patients, but the duration of remission was short (1-8.5 mo). CNS leukemia or hematological relapse occurred during relapse, and 5/6 patients died within 2 yr of treatment. The leukemia cells from the patients lacked surface immunoglobulin and receptors for mouse RBC but had receptors for complement (C3) and untreated sheep RBCs. High terminal deoxynucleotidyl transferase (TdT) activity was observed peripheral blood and bone marrow cells in 4/5 patients. Anterior mediastinal tumors were discovered at autopsy in two patients; dominant cells in these two patients were C3+. Because of similarities in cell surface markers, the T-precursor leukemia cells from the patients with ALL and early fetal thymocytes were thought to resemble each other in T-cell maturation. (28 Refs) (In JPN)

15. COMPARISON OF HLA PHENOTYPES IN LONG-TERM SURVIVORS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH IMMUNOTHERAPY VERSUS CHEMOTHERAPY.

Tursz T, Hors J, Lipinski M, Amiel JL, Mathe G
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Recent Results Cancer Res; 80:26-28 1982

Human leukocytic antigen (HLA) phenotypes were studied in children with acute lymphoblastic leukemia (ALL) who were alive without relapse greater than 8 yr after initiation of long-term chemotherapy (CT) or short-term chemotherapy followed by immunotherapy (IT). HLA determinations were of no prognostic value for CT patients. HLA AW33 and B17 antigens were increased significantly among IT patients, indicating prognostic value for HLA typing. (5 Refs)

16. MONOCLONAL ANTIBODIES REACTIVE WITH ACUTE MYELOGENOUS LEUKEMIA CELLS.

Linker-Israeli M, Billing RJ, Foon KA, Terasaki PI
1000 Veteran Ave., Room 15-22, Los Angeles, CA, 90024
J Immunol; 127(6):2473-2477 1981

Two cytotoxic monoclonal antibodies (D5D6 and C10H5) were raised to acute myelogenous leukemia (AML) cells. One of them, D5D6, reacted with 100% of the cells from 44/50 AML patients. The second, C10H5, reacted with 100% of the cells from 13/39 AML patients. D5D6 and C10H5 were cytotoxic to 100% of the monocytes from all healthy donors tested. Apart from monocytes, these antibodies did not react with any other peripheral blood cells from normal donors or with cancerous cells either from cell culture lines or from patients with chronic myelogenous leukemia (CML), lymphoid leukemias, or solid tumors. These antibodies inhibited the growth of the myeloid-monocytic stem cell, the CFU-C, and reacted with a minor population of normal bone marrow cells by immunofluorescence. Both D5D6 and CH5 have potential utility for the differential diagnosis of acute leukemia, for the detection of early leukemic relapse, and for enrichment of human stem cells. (Author abstract) (18 Refs)

17. DEFECTIVE IMMUNOREGULATORY T-CELL FUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Han T, Ozer H, Henderson ES, Dadey B, Nussbaum-Blumenson A Barcos M
Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Blood; 58(6):1182-1189 1981

Chronic lymphocytic leukemia (CLL) of B-cell origin results in the malignant proliferation of small Ig-bearing lymphocytes. There is currently a controversy in the literature regarding both the ability of this leukemic population to differentiate into mature plasma cells, as well as the ability of apparently normal T cells from these patients to regulate allogeneic B-cell differentiation. In the present study we have examined the lymphocytes of CLL patients in various clinical stages of their disease and with different surface phenotypes of their leukemic B-cell population. Our results show that leukemic CLL B cells from all 20 patients (including 1 patient with a monoclonal IgM paraprotein and another with a monoclonal IgG paraprotein) are incapable of further differentiation even in the absence of suppressor T cells and the presence of helper T lymphocytes. This lack of capacity to differentiate is unaffected by clinical stage, by therapy, or by the phenotype of the malignant population. Since the leukemic B population did not suppress normal allogeneic B-cell differentiation, the maturation deficit is evidently intrinsic to the leukemic clone rather than a result of activity of non-T suppressor cells. T helper function wa s also variably depressed in the blood of some patients with CLL, and this depression did not correlate with clinical stage, with therapy, or with the degree of lymphocytosis. Dysfunction of radiosensitive T suppressor cells was found to be the most consistent regulatory deficit of CLL T cells. Each of 11 patients whose leukemic cell population was of the mudelta, mualpha, or mu phenotype had both helper and suppressor cell defects. In contrast, three patients with gamma-bearing leukemic populations exhibited normal T helper as well as normal radiosensitive suppressor T-cell function. These results emphasize the heterogeneity of immunoregulatory T-cell function in patients with CLL and may indicate immunologically unique subgroups of patients with this malignancy. (Author abstract) (18 Refs)

18. CHRONIC LYMPHATIC LEUKEMIA OF B-CELL TYPE: CLINICAL AND MORPHOLOGICAL INVESTIGATIONS FOR DIAGNOSTIC DIFFERENTIATION.

Schwarzmeier JD, Radaszkiewicz T, Graninger W, Hofer F, Paietta E, Moser C
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Klin Wochenschr; 59(23):1313-1318 1981

Chronic lymphatic leukemia (CLL) was diagnosed in 71 patients based on clinical data. Most of the patients were in the stages 0, I and II; only 18% were in the stages III and IV according to Rai. In all cases, the disease was characterized by an increased number of B lymphocytes (B-CLL). The B cells mostly expressed a weak fluorescence intensity when tested for membrane bound immunoglobulins (Ig). In accordance to that, the quantitative measurement of Ig in the serum revealed a decrease of one or more Ig classes in 72% of the patients. No correlation existed between the number of B lymphocytes (and T lymphocytes) or the Ig concentration in the serum and the stage of the disease. To distinguish the CLL from related lymphoproliferative disorders, especially the immunocytic lymphoma, lymph node biopsies were examined histologically and immunomorphologically for intracytoplasmic Ig. This examination confirmed the diagnosis of CLL in 33 out of 40 cases. Six lymph nodes were classified as immunocytic lymphoma of the lymphoplasmacytoid type. In three of the latter, the immunocytic lymphoma was clinically associated with decreased Ig concentrations in the serum. These findings emphasize that the clinically established diagnosis of CLL should be corroborated by immunomorphology. (Author abstract) (26 Refs) (In GER)

19. IMMUNOLOGIC CHARACTERIZATION AND ULTRASTRUCTURAL CORRELATIONS FOR 125 CASES OF B- AND T-CELL LEUKEMIAS: STUDIES OF CHRONIC AND ACUTE LYMPHOCYTIC, PROLYMPHOCYTIC, LYMPHOSARCOMA CELL AND HAIRY CELL LEUKEMIA, SEZARY'S SYNDROME, AND OTHER LYMPHOID LEUKEMIAS.

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Cancer; 48(12):2630-2642 1981

Peripheral blood from 125 patients (160 specimens) with various types of lymphoid leukemias was evaluated for B- and T-cell markers (E rosettes, C3 and Fc receptors, and surface immunoglobulin). B-cell leukemias comprised 82% of the series and included chronic lymphocytic leukemia (69/71 cases), acute lymphocytic leukemia (1/18 cases), lymphosarcoma cell leukemia (15/18 cases), prolymphocytic leukemia (1 case), plasma cell leukemia (1 case), hairy cell leukemia (12/12 cases), and the leukemic phase of 'histiocytic' lymphoma and Waldenstrom's macroglobulinemia (1 case each). Within the B-cell group, certain leukemias exhibited distinct patterns of lymphocyte surface markers. Three cases of lymphosarcoma cell leukemia revealed both T and B cell markers (E-rosette formation and monoclonal SIg). T-cell leukemias comprised 12% of the series and included chronic lymphocytic leukemia (2/71 cases), acute lymphocytic leukemia (11/18 cases), and Sezary's syndrome (2/2 cases). In eight cases of acute lymphocytic leukemia, the majority of the cells demonstrated no definable markers (non-B, non-T cell type). Ultrastructural studies, performed in selected cases, were correlated with immunologic findings. Distinctive morphologic features were observed for different variants of B- and T-cell leukemias. Neoplastic cells of T-cell leukemias revealed a greater nuclear irregularity than B-cell proliferations, as assessed by the nuclear contour index (ratio of circumference to the square root of the nuclear area). The cytoplasmic feature most predictive of immunologic cell type was abundant rough endoplasmic reticulum, suggesting plasmacytoid differentiation, observed in some B-cell proliferations. (Author abstract) (70 Refs)

20. IMMUNOREGULATION BY BLASTS FROM NULL CELL AND T-CELL LEUKEMIAS: HELP AND SUPPRESSION OF T-CELL PROLIFERATIVE RESPONSES TO MITOGENS.

Kaur P, Schulof RS, Miller DR, Steinherz P, Good RA, Gupta S
(c/o Gupta), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10012
Cancer; 49(1):43-47 1982

The immunoregulatory activity of bone marrow leukemic blasts from five patients with null-cell acute lymphoblastic leukemia (ALL) and two children with T-cell ALL was evaluated. Blasts were studied in co-culture for their effects on the proliferative responses of normal allogeneic peripheral blood lymphocytes to phytohemagglutinin. Mitomycin C-treated null cell ALL blasts from two of five children suppressed the proliferative responses of normal responder cells by 80% and 58% whereas those from two other children enhanced the responses by 118% and 31%. T-cell leukemic blasts from one patient with T-cell ALL exhibited helper cell activity (26%) and T-leukemic blasts from the other demonstrated suppressor cell activity (53%). The helper cell activity of leukemic blasts was associated with stimulating capa city of null blasts in one-way mixed lymphocyte reactions. In six of seven cases, incubation of blast cells with concanavalin A (20 ug/ml) for 48 hr prior to co-culture with responder cells did not result in the generation of significant suppressor cell activity. Our study suggests that leukemic blasts from certain patients with 'null' and T-cell ALL may possess spontaneous helper or suppressor cell immunoregulatory activity. The functional heterogeneity of leukemic blasts may help in subclassifying the ALL. (Author abstract) (22 Refs)

21. 10. POSSIBLE MECHANISMS OF IMMUNOTHERAPY ACTION IN ACUTE NONLYMPHATIC LEUKEMIA: MACROPHAGE PRODUCTION OF COLONY-STIMULATING ACTIVITY.

Reizenstein P, Andersson B, Beran M
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Recent Results Cancer Res; 80:64-69 1982

Earlier studies show that immunotherapy (IT) improves prognosis in acute nonlymphatic leukemia (ANLL), and that ANLL cells probably have tumor-associated antigens, for autologous lymphocytes can react to them. Also, IT seems to immunize against allogeneic ANLL cells, but there is no cross-immunity to autologous ones. Moreover, patients immunized against their ANLL cells have no better prognosis than patients not having lymphocytes reacting to their ANLL cells. It has also been suggested that IT causes nonspecific immunostimulation, but IT patients' lymphocytes actually react less than those of patients not given IT. The current hypothesis is macrophage activation: Lymphocyte suppression in IT could be explained by suppressor macrophages. Colony-stimulating activity, produced by bone marrow macrophages, decreases during remission in patients not given IT, but not in IT patients. Numerically, blood cells from patients given IT form more colonies than those from patients not given IT. Three of

eight patients given IT had more colonies than the upper normal limit. (Author abstract) (16 Refs)

22. 8. THERAPEUTIC EFFECTIVENESS OF NEURAMINIDASE-TREATED ALLOGENEIC MYELOBLASTS AS IMMUNOGEN IN ACUTE MYELOCYTIC LEUKEMIA.

Bekesi JG, Holland JF
Dept. Neoplastic Diseases, City Univ. New York, Mount Sinai Sch. Medicine and Hosp., New York, NY, 10029
Recent Results Cancer Res; 80:42-55 1982

Our chemoimmunotherapy study shows significantly longer remission and survival in acute myelocytic leukemia (AML) patients who have been immunized with neuraminidase-treated allogeneic myeloblasts as compared to patients who received chemotherapy alone or neuraminidase-treated myeloblasts plus MER. MER impairs the immunotherapeutic effectiveness of neuraminidase-treated allogeneic myeloblasts in AML patients. The in vivo and in vitro immunologic status in each arm of the protocol correlate well with the duration of remission and survival of the patient. (Author abstract) (22 Refs)

CHEMOTHERAPY

23. 13. PREVENTION OF BLASTIC CRISIS IN PH(1)-POSITIVE CHRONIC MYELOID LEUKEMIA.

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Recent Results Cancer Res; 80:78-82 1982

Fourteen untreated patients with Ph(1)-positive chronic myeloid leukemia received combination chemotherapy consisting of blocks of doxorubicin, vincristine, cytosine arabinoside and 6-thioguanine. Significant karyotypic conversion occurred in six patients, the percentage of Ph(1)-positive cells in the bone marrow falling by at least 50%. Maintenance therapy comprised vincristine, busulfan hydroxyurea, 6-mercaptopurine and dibromannitol in rotation. Reinduction therapy was administered when Ph1 positivity reverted to 100%. Karyotypic reconversion was achieved in three of four patients. After induction, chromosome analysis of the bone marrow was performed every 3-6 mo to detect the appearance of aneuploid clones, the intention being to intensify therapy at that stage. (Author abstract) (10 Refs)

24. TREATMENT OF ACUTE MYELOCYTIC LEUKEMIA: A STUDY BY CANCER AND LEUKEMIA GROUP B.

Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, Preisler HD, Nawabi IW, Prager D, Carey RW, Cooper MR, Haurani F, Hutchison JL, Silver RT, Falkson G, Wiernik P, Hoagland HC, Bloomfield CD, James GW, Gottlieb A, Ramanan SV, Blom J, Nissen NI, Bank A, Ellison RR, Kung F, Henry P, McIntyre OR, Kaan SK
Div. Hematology/Oncology, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY, 11042
Blood; 58(6):1203-1212 1981

In a randomized study of acute myelocytic leukemia (AML), 352 patients of all ages were treated for remission induction by one of the four regimens: 7 days of cytosine arabinoside (ara-C) by continuous iv infusion or bolus injection every 12 hr, together with daunorubicin (DNR) by rapid iv injection on days 1, 2, 3; or 5 days of ara-C by infusion or bolus injection and DNR for 2 days only. The regimen of 7 and 3 infusion was significantly superior to the other three regimens, resulting in 56% complete remission (CR). For remission maintenance, ara-C was given for 5 days every mo and each mo one of the following four drugs added on a cyclic rotational basis: thioguanine, cyclophosphamide, lomustine (CCNU), or DNR. Although ara-C dosage each month was the same, the route of ara-C administration by random allocation was either rapid iv bolus or sc injection. The median duration of CR was significantly longer for sc ara-C group: 14 mo for patients less than 60 yr old (versus 8 mo for iv) and 31 mo for 60 or older age group (versus 9 mo for iv). Patients who received a combination of the best of the four induction regimens (7 and 3 infusion) and the better of the two maintenance schedules (sc ara-C) had a median remission duration of 22 mo an d a median survival of 35 mo (the longest reported in a prospective randomized trial of therapy for AML). These results establish the validity of an intensive chemotherapy to produce rapid marrow aplasia followed by a sequential maintenance therapy for achieving prolonged disease-free survival in AML. (Author abstract) (37 Refs)

25. PHASE I STUDY ON 5-AZA-2'-DEOXYCYTIDINE IN CHILDREN WITH ACUTE LEUKEMIA.

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Leuk Res; 5(6):453-462 1981

A Phase I study of 5-aza-2'-deoxycytidine (5-AZA-CdR) was conducted in children with advanced leukemias refractory to conventional therapy. The starting dose of 5-AZA-CdR was 0.75 mg/kg, administered as a 12-hr iv infusion. The dose was increased stepwise until a plasma concentration was obtained that produced significant anti-leukemia activity; this was followed by stepwise increases in duration of infusion. At a dose of 20 mg/kg, the 5-AZA-CdR produced no observable toxicity. At doses of 24 and 30 mg/kg, mild nausea, vomiting, and diarrhea were noted. Alopecia occurred in some patients receiving two or more treatments with 36-50. 5-AZA-CdR at 36 or 80 mg/kg and administered as a 40-hr infusion produced marked granulocytopenia and thrombocytopenia in children with solid tumors. Hematopoietic toxicity was difficult to determine in the leukemia patients because of the presence of greater than 90 leukemic blasts in the marrow. At low doses of the 5-AZA-CdR (0.75-17 mg/kg), the antileukemic effect was short-lived, while at higher doses (24 mg/kg, 24-hr infusion or 30 mg/kg, 30-hr infusion), the drug produced longer reduction of leukemic blasts. The 5-AZA-CdR produced a very potent antileukemic effect in some patients when the dose was increased to 36 mg/kg and the infusion time was increased to 36 hr. A clearing of meningeal leukemia was observed in two patients who received 5-AZA-CdR at a dose of 44 mg/kg for 44 hr or 80 mg/kg for 40 hr. The kinetics of normal bone marrow recovery after treatment of two leukemic patients with 5-AZA-CdR at 36 mg/kg over 36 hr are described. In vitro drug sensitivity data on leukemic cells of blood and marrow at different times during treatment of patients with the 5-AZA-CdR showed resistance in some of the patients. Concentrations of 5-AZA-CdR in plasma and cerebral spinal fluid were measured. (23 Refs)

26. CENTRAL NERVOUS SYSTEM TOXICITY OF HIGH-DOSE SYSTEMIC CYTOSINE ARABINOSIDE.

Lazarus HM, Herzig RH, Herzig GP, Phillips GL, Roessmann U, Fishman DJ

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Cancer; 48(12):2577-2582 1981

Forty-nine adult patients with acute leukemia in relapse, refractory to conventi onal therapy, were studied. Increasing quantities of iv bolus high-dose cytosine arabinoside (cytarabine) were administered using the following schedules: 3 g/m2 every 12 hrs for 4-16 consecutive doses, or 4.5 g/m2 every 12 hrs for 12 consecutive doses. Patients ages ranged 16/76 yrs (median: 38). Thirty-seven patients had previously received either induction or maintainance therapy with conventional doses of cytarabine. Cerebral or cerebellar dysfunction attributable to cytarabine was observed in eight patients and appeared 6-8 days (mean: 6.6) after the first dose and lasted 3-7 days (mean: 4.7). None of 12 patients receiving up to 24 g/m2 total dose exhibited CNS toxicity; three of 19 receiving a total dose of 36 g/m2 and one of 12 patients given a total dose of 48 g/m2 developed reversible neurologic dysfunction. Four of six patients receiving 54 g/m2 developed CNS toxicity (irreversible in two cases), a significantly greater incidence compared to toxicity in patients receiving less than or equal to 48 g/m2 total dose (p less than 0.01). CNS toxicity was dose-related since patients treated for 12 consecutive doses of 4.5 g/m2 had significantly greater CNS toxicity than 12 consecutive doses at 3 g/m2 (p less than 0.04). Systemic cytarabine doses less than 54 g/m2 can be administered with minimal CNS side-effects. (Author abstract) (48 Refs)

27. DIFFUSION CHAMBER CULTURES OF BONE MARROW CELLS IN REFRACTORY ANEMIA WITH EXCESS OF BLASTS (RAEB).

Izzi T, Fontebuoni A, Falevi N, Lucarelli G

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Haematologica (Pavia); 66(5):570-578 1981

The effects of chemotherapy on blast cells in refractory anemia with excess of blasts (RAEB) and on bone marrow cells of acute nonlymphoid leukemia (ANLL) were evaluated by means of diffusion chamber (DC) cultures. For RAEB patients, the av growth before chemotherapy was slightly above the normal range. Treated patients showed an inhibition of growth in DC as compared to normal ones. In bone marrow cultures from 6/8 ANLL patients, an increase in cellular concentration was noted during the DC culture period. In four ANLL patients studied during remission, the bone marrow cells cultured in DC did not demonstrate any growth either above normal values or above DC growth before treatment. Cultures of bone marrow from RAEB patients before therapy showed a moderate increase in granulocytic maturation and mature cells and in macrophages and cultures of marrows from ANLL patients showed a noticeable increase of mature granulocytes with frequent signs of degeneration. A suppression of granulocyte growth and differentiation was observed during remission. The results of the study suggest that in RAEB treatment the DC technique can be of limited value and that all forms of leukemic chemotherapy must be avoided in the RAEB syndrome unless the p atient has overt leukemia. (9 Refs)

RADIOTHERAPY

28. IRRADIATION OF THE THYMUS REGION IN CHRONIC LYMPHOID LEUKEMIA. SEVEN CASES.

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Nouv Presse Med; 10(39):3227-3229 1981

Seven patients with chronic lymphatic leukemia, B type, have been treated with thymic irradiation. A full remission was achieved in two and a partial one in four. No serious complications were noted during or after the irradiation. This treatment has proved efficient even after the failure of a previous chemotherapy and has permitted the resumption of any other therapeutic modality when the CLL is no more controlled. (Author abstract) (9 Refs) (In FRE)

29. PITUITARY FUNCTION AND GROWTH OF CHILDREN UNDER LEUKEMIA TREATMENT.

Schuler D, Gacs G, Revesz T, Koos R, Keleti J

II. Gyermekklinika, Semmelweis Orvostudomanyi Egyetem, Tuzolto u. 7-9, H-1094 Budapest, Hungary

Monatsschr Kinderheilkd; 128(12):773-775 1981

The effect of cranial irradiation (total dose 2,400 or 4,800 rads, individual dose 150 wk within 3 wk) on the pituitary function of 40 children (2-14 yr old) with acute lymphoblastic leukemia was studied 1-3 yr after radiotherapy. Corticosteroids were not administered. The plasma growth hormone level, determined after arginine stimulation in 15 children, was normal in 13. The basal thyroid stimulating hormone level was normal in all cases, but its rise following administration of thyrotropin-releasing hormone was subnormal in 13/15 cases. The patients with subnormal growth hormone levels and subnormal thyroid stimulating hormone levels were not identical. The increase in the urinary excretion of ketogenic steroids under the effect of metyrapone was normal in all cases. The growth, monitored in 40 children, was normal in all cases compared with that of healthy controls. (11 Refs) (In GER)

SURGERY

30. SPLENIC RUPTURE IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES.

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Cancer; 48(12):2729-2733 1981

Five cases of pathologic rupture of the spleen in patients with hematologic malignancy are presented along with a review of the 48 cases previously described in the English literature. Pathologic splenic rupture occurred most commonly in patients with acute leukemia but has been well documented in chronic leukemias and in lymphoma as well. Nearly all patients experience abdominal pain at the time of rupture; however, this pain was frequently confused clinically with that of biliary tract obstruction, aortic aneurysm, perforated viscus, pancreatitis, and angina pectoris. Pain referred to the left shoulder (Kehr's sign) was present in only 17% of patients. Hypotension was documented in 66%, fever in 74%, and tachycardia in 75%. The most effective diagnostic procedure was paracentesis, which confirmed intraabdominal hemorrhage in each of the

nine cases in which the procedure was used. A correct preoperative diagnosis of splenic rupture was reported in only 10 of the 53 cases reviewed. Fifty-two percent of the patients underwent laparotomy; 48% died without operation. Of those that underwent surgery, 78% survived the procedure and the immediate postoperative period. The survival rate of all patients was 38%. There was no correlation of the type of hematologic malignancy, occurrence or type of treatment, peripheral blood counts, or spleen size to survival. The most important factor in predicting survival was appropriate surgery. (Author abstract) (38 Refs)

OTHER THERAPEUTIC MODALITIES

31. THE EFFECTS OF GLUCOCORTICOID THERAPY ON GLUCOCORTICOID RECEPTORS IN LEUKEMIA AND LYMPHOMA.

Shipmen GF, Bloomfield CD, Smith KA, Peterson BA, Munck A (c/o Bloomfield), Univ. Minnesota Hosp., Box 277, Minneapolis, MN, 55455
Blood; 58(6):1198-1202 1981

Measurement of glucocorticoid receptors appears to be useful for selecting which patients with leukemia and lymphoma should receive glucocorticoid therapy. To determine the effect of recent or concurrent glucocorticoid therapy on the number of measured tumor glucocorticoid receptor sites, 18 patients with leukemia and lymphoma were studied. Baseline determinations of numbers of glucocorticoid receptors were performed on the malignant cells circulating in the patients' peripheral blood. Glucocorticoid therapy was then instituted consisting of dexamethasone 4 mg po every 6 hr. Repeat determinations of the number of glucocorticoid receptor sites were performed within 24 hr and at various subsequent times from the start of therapy. When compared to baseline receptor numbers, 16 of the 18 patients demonstrated a decrease in receptor number (median decrease 1,651 sites/cell) after the start of glucocorticoid therapy. The magnitude of the change in receptor number was independent of the initial number of receptors. Our results suggest that in order to accurately interpret glucocorticoid receptor numbers in patients with leukemia and lymphoma, glucocorticoid should not be administered for 3 wk prior to determinations of receptor levels. (Author abstract) (11 Refs)

MULTIMODAL THERAPY

32. 11. THE FINNISH LEUKAEMIA GROUP: LEVAMISOLE IN MAINTENANCE THERAPY OF ACUTE MYELOID LEUKEMIA IN ADULTS.

Lehtinen M, Ahrenberg P, Hanninen A, Ikkala E, Lahtinen R, Levanto A, Palva I, Rajamaki A, Rosengard S, Ruutu T, Sarna S, Selroos O, Timonen T, Waris E, Wasastjerna C, Vilpo J, Vuopio P
Tampere Central Hosp., SF-33520 Tampere 52, Finland
Recent Results Cancer Res; 80:70-72 1982

The Finnish Leukemia Group has carried out a randomized, multicenter trial to study the effect of levamisole on the remission maintained with 6-mercaptopurine and methotrexate in acute myeloid leukemia in adults. Levamisole was given on 3 consecutive days every 2 wk. Twenty-five patients received only chemotherapy, while 26 patients received levamisole as well. The patients receiving levamisole showed significantly better remission duration than those given only chemotherapy ($p = 0.033$, Mantel's summary X(2)-test). There are four long term survivors in the levamisole group versus none in the chemotherapy group. The remissions have lasted 48-75 mo. (Author abstract) (8 Refs)

33. HAIRY CELL LEUKEMIA: CLINICAL EFFECTS OF THE METHANOL EXTRACTION RESIDUE (MER) OF BCG, LITHIUM CARBONATE AND MONONUCLEAR CELL-ENRICHED LEUKOCYTE TRANSFUSIONS.

Quesada JR, Hersh EM, Keating M, Zander A, Hester J
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Leuk Res; 5(6):463-476 1981

The effect of mononuclear cell-enriched WBC transfusions (MNCTs) alone or in combination with iv methanol extraction residue (MER) was studied in 11 men (37-61 yr old) who had hairy cell leukemia (HCL). The combination of MER an lithium carbonate (LC) also was examined. Of eight patients receiving the MER alone, two had a minimal hematologic response (MHR). Of four patients receiving LC and MER, one showed an MHR. Of seven evaluable patients who received MNCTs, four achieved a response (2 complete and 2 partial). The incidence of infection observed after therapy did not differ significantly from that observed before therapy. Side effects of the MER treatment included fever (usually lasting 24 hr), chills and malaise, mild dyspnea or dry cough, and polyarthralgia. Side effects of the LC treatment included dizziness, distal tremor and lightheadedness. Two patients developed acute maculopapular rash in association with the MNCT treatment. The results indicated that favorable hematological effects can be produced following hematopoietic manipulation intended to enhance proliferation and maturation of bone marrow precursor cells. (51 Refs)

34. 9. MAINTENANCE CHEMOIMMUNOTHERAPY OF NONLYMPHOBLASTIC ACUTE LEUKEMIAS.

Favre R, Sebahoun G, Bagarry-Liegey D, Imbert C, Ciardelli P, Gastaut JA, Meyer G, Carcassonne Y
Institut J. Paoli, I. Calmettes, 232 Boulevard de Ste. Marguerite, F-13009 Marseille, France
Recent Results Cancer Res; 80:56-63 1982

A trial of maintenance chemotherapy of nonlymphoblastic acute leukemia led to a comparison of two groups of patients in complete remission. Group 1 (14 patients) received only monthly reinduction chemotherapy. Group 2 (17 patients) received identical chemotherapy together with weekly immunotherapy combining BCG and irradiated leukemic cells. While the duration of the first complete remission was unmodified, the overall survival time and, above all, survival after the first relapse were prolonged in Group 2 chemoimmunotherapy. These results were all the more marked when a homogeneous group of patients having received the same induction chemotherapy were considered. (Author abstract) (15 Refs)

35. RANDOMIZED CLINICAL TRIAL OF IMMUNOTHERAPY AND ANDROGENOTHERAPY FOR REMISSION MAINTENANCE IN ACUTE NON-LYMPHOCYTIC LEUKEMIA.

Mandelli F, Amadori S, Dini E, Grignani F, Leoni P, Liso V, Martelli M, Neri A, Petti MC, Ferrini PR
Istituto di Ematologia, Universita di Roma, Via Chieti 7, 00161 Rome, Italy
Leuk Res; 5(6):447-452 1981

A randomized study of 212 consecutive, previously untreated acute nonlymphocytic leukemia (ANLL) patients was conducted to determine if the addition of BCG and/or stanozolol (STZ) to cyclic chemotherapy (CT) produces longer remissions than maintenance with CT alone. All patients received the same induction CT (daunomycin, cytarabine, and thioguanine; 3 courses). When complete remission was achieved, the patients received consolidation CT (adriamycin and cytarabine; alternating courses; 2 mo). Patients who were in complete remission at the end of consolidation CT were allocated to one of four therapy regimens: CT alone (A), CT plus BCG (B), CT plus STZ (C), or CT plus BCG and STZ (D). Eighty-two patients (42 males, 40 females; 7-74 yr old) were randomized to the maintenance arms. The median duration of remission was 64 wk for regimen A, 65 for B, 42 for C, and 54 for D, the the differences between the remission duration curves were not statistically significant. Five patients (2 in regimen B, 1 in each of regimens A, C, and D) completed therapy and were in remission 12 mo after discontinuing therapy. Fifty-six relapses (51 bone marrow, 1 CNS, 1 skin, 1 testis, and 1 breast) were reported. The median survival for the 82 randomized patients was 92 wk. Toxic manifestations to therapy are described. The results indicated that BCG immunotherapy and/or androgenotherapy used in combination with maintenance CT does not prolong the duration of remission. (28 Refs)

36. ADJUVANT SPECIFIC IMMUNOTHERAPY IN MAINTENANCE TREATMENT OF ADULT ACUTE NON-LYMPHOCYTIC LEUKEMIA.

Ruhl H, Fulle HH, Koeppen KM, Schwerdtfeger R
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Klin Wochenschr; 59(21):1189-1193 1981

From 1976 until 1978, 136 adult patients with acute leukemia were treated in four hospitals in Berlin. A complete remission was achieved in 47 patients (35%). Twenty-six patients with non-lymphocytic acute leukemia, who had achieved a complete remission with induction chemotherapy consisting of daunorubicin (45 mg/m2day, day, 1, 2 and 3) and cytosine-arabinoside (100 mg/m2/day, continuous infusion, day 1 to day 7) were entered into a randomized trial. Thirteen patients were treated with an intermittent combination chemotherapy at 4-wk intervals; the other group of patients received in addition a specific immunotherapy consisting of neuraminidase-modified allogeneic blast cells. The results revealed that the addition of this kind of immunotherapy did not increase the duration of first remission or survival. (Author abstract) (21 Refs)

37. ENDOCRINE ASSESSMENT IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA.

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Cancer; 49(1):145-151 1982

Ten children ages 7 to 18 (8 girls, 2 boys) with acute lymphoblastic leukemia (ALL) were studied. Remission was induced with prednisone, vincristine, and asparaginase followed by preventive central nervous system treatment with 2,400 rads cobalt-60 cranial irradiation plus intrathecal methotrexate. At the time of study all patients had been on continuation chemotherapy with two to four drugs for 2 to 2 1/2 years. Three patients were on mercaptopurine and methotrexate, one was on cyclophosphamide in addition, and six were on these drugs plus arabinosyl cytosine. Linear growth and bone age for height was appropriate in all. Tests included oral glucose (OGTT) and tolbutamide (TOLB) tolerance tests, ACTH infusion, thyroid function and measurement of noctural growth hormone (IRGH), and cortisol. All patients tested (9/10) had a normal OGTT. Peak glucose and insulin (IRI) values occurred at 30 minutes in 8/9 subjects (IRI range 24-143 uU/dl). IRGH responses to sleep, TOLB and following OGTT were greater than 5 ng/ml in at least one test in all, with 5/10 patients responding above this level in all three tests. Diurnal variation of cortisol was observed in all patients (8/10) studied. Thyroid function and response to ACTH was normal in all patients. No consistent changes were observed in gonadotropins. It is concluded from these results that hypothalamic pituitary function appeared to be intact despite 2,400 rads of cobalt-60 cranial radiation and ongoing chemotherapy for ALL in 10 patients observed. Long-term studies are required to exclude late endocrine complications in such children. (Author abstract) (25 Refs)

SUPPORTIVE CARE

38. 12. TREATMENT OF ACUTE LEUKEMIA IN REMISSION BY BONE MARROW TRANSPLANTATION.

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Recent Results Cancer Res; 80:73-77 1982

Before 1975 only patients with chemotherapy-refractory acute leukemia were treated by marrow transplantation. The preparative regimen developed in Seattle consisted of cyclophosphamide follo wed 2-3 days loter by 1,000 rad total body irradiation from two opposing cobalt sources and a marrow transplant from an HLA-identical sibling. Of the first 100 patients, 13 were alive in unmaintained remission 5.5-10 yr after transplantation with functioning marrow grafts. In this initial series of patients leukemic recurrence was one of the major problems. Attempts to reduce recurrent leukemia by the use of more aggressive antileukemic regimens before transplantation were unsuccessful. In early 1976 a study of acute leukemia patients transplanted in remission was begun. Twenty-two patients with acute lymphoblastic leukemia were transplanted in second, third, or subsequent remission and 8 (35%) are now in unmaintained remission 2.5-4.5 yr later. Recurrent leukemia was the cause of death for 11 patients in the acute lymphoblastic leukemia group. Twelve of the first 19 patients with acute nonlymphoblastic leukemia grafted in first remission are now alive and well in unmaintained remission 2-4 yr after transplantation. At present 48 patients have been included in the study and 31 (65%) are living in remission. Only one of the 48 patients has had a recurrence of leukemia. The principal causes of death were graft-versus-host disease and interstitial pneumonia. Marrow transplantation for patients with chronic myelogenous leukemia in blast crisis had resulted in one unmaintained remission surviving now, at 4.5 yr, among six patients with syngeneic grafts and four long-term survivors (8, 15, 27, and 31 mo)

among 22 patients with allogeneic grafts. Three of four patients with chronic myelogenous leukemia in chronic phase given syngeneic transplants are now in remission with lack of Philadelphia chromosome at 3-4 yr, while one had reappearance of the Philadelphia chromosome at 2.5 yr and is now surviving in the chronic phase. (Author abstract) (11 Refs)

39. BONE MARROW TRANSPLANTATION IN ACUTE LEUKEMIAS: PROPHYLACTIC ANTIBODY TREATMENT FOR SUPPRESSION OF GRAFT-VERSUS-HOST DISEASE.

Rodt H, Netzel B, Kolb HJ, Haas RJ, Wilms K, Bender-Gotze C, Wernet P, Janka G, Link H, Wilmanns W, Thierfelder S, Munchner Arbeitsgemeinschaft fur KMT
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Blut; 43(2):113-118 1981

Suppression of graft-vs-host disease (GvHD) by antibody treatment was tested in patients with acute leukemias who had received bone marrow transplants. Anti-human T-cell-globulin (AHTZG) was prepared by adsorption of anti-human-thymocyte serum with liver/kidney homogenate, B cells from patients with chronic leukemia, and erythrocytes. The AHTZG was active against T-lymphocytes, but not against hemopoietic precursor cells in culture and diffusion-chamber assays. Patients were preconditioned by anti-leukemic chemotherapy and whole-body irradiation of 1,000 rads. Marrow transplants were obtained from compatible siblings. Ten patients were in relapse, and four were in remission at the time of transplant. Hemopoietic grafts were successful in 12 cases. No side effects were noted. Three patients showed cutaneous signs of GvHD, and two of them later developed GvHD in the liver. Five of 14 patients were alive and in remission 144-964 days after transplant. (14 Refs) (In GER)

40. ASPERGILLUS PERICARDITIS: CLINICAL AND PATHOLOGIC FEATURES IN THE IMMUNOCOMPROMISED PATIENT.

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Cancer; 49(1):48-54 1982

There has been a proliferation of infectious complications due to Aspergillus in patients receiving chemotherapy for cancer and transplantation; however, aspergillus pericarditis has been rarely described. Reported here are the clinical and pathologic findings of Aspergillus pericarditis in six immunocompromised patients who came to autopsy in the past 11 yr. Five had leukemia, one had received a renal transplant. All had pulmonary aspergillosis. Two had clinically overt pericarditis leading to cardiac tamponade and death. Pulmonary aspergillosis preceded development of pericardial signs. Chest radiographs, serial electrocardiograms, and echocardiograms showed abnormality but were nonspecific. Pericardiocentesis was performed in one patient but proved nondiagnostic and yielded only transient hemodynamic improvement; postmortem Gram stain of the spun sediment of that pericardial fluid revealed branched hyphae. Although five patients received Amphotericin B, whether it entered the pericardial space is uncertain. Postmortem examination revealed extensive pericardial involvement by Aspergillus associated with effusions as large as 1,000 ml Aspergillus penetrated the pericardium by rupture of myocardial abscesses and invasion from contiguous pulmonary foci into the pericardial space. A clinical diagnosis of Aspergillus pericarditis was never established, and at least two died of their pericardial disease. Aspergillus pericarditis is a lethal cardiac infection, which is likely to increase in frequency, and should be considered in the hemodynamically unstable immunocompromised patient especially when signs of pericarditis or pulmonary aspergillosis are present. (Author abstract) (28 Refs)

41. FAILURE OF ORAL TRIMETHOPRIM-SULFAMETHOXAZOLE PROPHYLAXIS IN ACUTE LEUKEMIA. ISOLATION OF RESISTANT PLASMIDS FROM STRAINS OF ENTEROBACTERIACEAE CAUSING BACTEREMIA.

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N Engl J Med; 306(1):16-20 1982

Two leukemia patients in whom fatal bacteremia with resistant Enterobacteriaceae occurred during po trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis are described. and the results of experiments designed to investigate the genetic basis of this antibiotic resistance are presented. Three strains of TMP-SMX-resistant Enterobacteriaceae were isolated from the blood of the two patients. Two strains contained a self-transmissible R plasmid specifying resistance to both trimethoprim and sulfamethoxazole. These results suggest that in vivo transfer can occur and that spread of resistance is likely. This dissemination of resistance would compromise the efficacy of TMP-SMX in preventing infection with Enterobacteriaceae in patients with granulocytopenia. In addition, the plasmids also specified resistance to ampicillin and carbenicillin. Widespread prophylactic use of TMP-SMX in patients with cancer will depend on careful monitoring for antibiotic-resistance plasmids. (19 Refs)

42. EFFICACY OF THE TOBRAMYCIN-COTRIMOXAZOLE-CEPHALOTHIN COMBINATION FOR FEBRILE EPISODES IN LEUKEMIC PATIENTS WITH GRANULOCYTOPENIA.

Mozzana R, Cortelezzi A, Radaelli F, Polli E
via Griziotti, 1, 20100 Milan, Italy
Haematologica (Pavia); 66(5):634-644 1981

A series of 48 febrile episodes in neutropenic patients with acute leukemia were treated with a combination of tobramycin, cotrimoxazole, and cephalothin (TTC). Results of the treatment were compared with those obtained in 46 febrile episodes in the same type of patients treated with antibiotics. The antibiotic combinations always included an aminoglycoside and carbenicillin combined with cephalosporin and/or semisynthetic penicillin and tetracycline (VAC regimens). In 79/94 febrile episodes, there was evidence of an infective process. Positive responses to therapy were obtained in 38/48 of the TCC cases (79.2%). In 20/46 of the VAC cases (43.5%), positive responses were obtained. The best response to therapy was observed in febrile episodes in patients with acute lymphocytic leukemia where 7/7 patients treated with TCC responded positively to therapy. Positive responses in the TCC-treated group was not correlated with the number of circulating neutrophils as was the case with the VAC-treated group. (23 Refs)

43. DURAL SINUS THROMBOSIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Steinherz PG, Miller LP, Ghavimi F, Allen JC, Miller DR
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
JAMA; 246(24):2837-2839 1981

Dural sinus thrombosis developed in two children with acute lymphoblastic leukemia during induction treatment with vincristine sulfate, prednisone, and asparaginase. Headache, nausea, emesis, and lethargy were the presenting signs. The diagnosis was confirmed by arteriography. The cause is presumed to be secondary to hypercoagulability due to asparaginase-induced antithrombin III deficiency. The patients received anticoagulation therapy and recovered completely. Only two of the six reported patients without heparinization survived. (Author abstract) (26 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

44. ACUTE MYELOCYTIC LEUKEMIA IN TWO BROTHERS WITH POLYPOSIS COLI AND CARCINOMA OF THE COLON.

Greenberg MS, Anderson KC, Marchetto DJ, Li FP
Mount Auburn Hosp., 416 Doctors' Office Building, 300 Mount Auburn St., Cambridge, MA, 02138
Ann Intern Med; 95(6):702-703 1981

Two brothers developed multiple adenomatous polyps of the colon and colonic adenocarcinoma, the classic features of familial polyposis coli. Both also developed acute myelocytic leukemia. This constellation of neoplasms is distinct from other genetic syndromes that feature polyposis coli. The parents of the brothers are first cousins, suggesting autosomal recessive inheritance of these multiple neoplasms. Autosomal dominant or X-linked transmission is also possible and should be evaluated in other affected families. (Author abstract) (7 Refs)

SELECTED PRE-CLINICAL STUDIES

45. HUMAN LYMPHOCYTE SURFACE ANTIGENS. PART 1. PRODUCTION AND CHARACTERIZATION OF HETEROANTISERA AGAINST CELL LINES DERIVED FROM T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND ADULT T-CELL LEUKEMIA.

Yoshimoto S
Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan
Nippon Ketsueki Gakkai Zasshi; 44(6):1153-1162 1981

Two heteroantisera were produced by immunizing NZW rabbits with cells of TALL-1 or MT-1. These antisera were rendered T-cell specific after absorption with human RBC acute myelogenous leukemia cells, surface Ig-positive chronic lymphocytic leukemia cells and several non-T lymphoblastoid cell lines. Absorbed antisera, anti-TALL-1 and anti-MT-1, were tested for reactivities with normal and malignant T-cells and cells of other hematological malignancies by indirect membrane immunofluorescence. Anti-TALL-1 and anti-MT-1 were uniformly reactive with normal thymocytes and peripheral blood T-lymphocytes, and their reactivities against these two populations of T-cells were almost completely abolished by absorption with normal thymocytes or peripheral blood lymphocytes (pbl). However, different reactivities were observed between these antisera. (1) Anti-TALL-1 was highly reactive with cells of T-ALL cell lines but only minimally with MT-1 and ATL cells. On the other hand, anti-MT-1 was highly reactive with MT-1 and ATL cells whereas its reactivities with cells of T-ALL cell lines were variable (10-67%). (2) Absorption of anti-TALL-1 with MT-1 cells eliminated reactivities with ATL cells but not with normal thymocytes and pbl. Similarly, absorption of anti-MT-1 with TALL-1 cells eliminated reactivities with T-ALL cell lines but not with normal thymocytes and pbl. There seems to be at least two distinct differentiation antigens in the normal T-cell series. One is recognized by anti-TALL-1 and the other by anti-MT-1. Antigens of T-ALL and ATL cells are distinct from those of normal T-cells. Antigens of ATL cells are homogeneous while those of T-ALL cells more heterogeneous and thus T-ALL may be further divided into subgroups. (44 Refs) (In JPN)

46. CHEMOTHERAPY OF L1210 LEUKEMIA WITH 5-AZACYTIDINE IN COMBINATION WITH VINCRISTINE, ADRIAMYCIN, OR BETA-CYTOSINE ARABINOSIDE.

Presant CA, Vietti TJ, Valeriote F, Coulter DM
Dept. Medical Oncology, City Hope Natl. Medical Center, 1500 East Duarte Rd., Duarte, CA, 91010
JNCI; 67(6):1283-1288 1981

The cytotoxicity of vincristine (VCR), beta-cytosine arabinoside (Ara-C), or adriamycin (ADRIA) in combination with 5-azacytidine (Aza-CR) to L1210 leukemia in vivo was measured to determine if schedule-dependent synergistic or antagonistic drug interaction occurred. Two dose levels of Aza-CR were studied (0.1 and 0.5 mg/mouse), and cytotoxicity was measured by the spleen colony assay. For the combination of Aza-CR plus VCR, cytotoxicity was essentially additive or antagonistic when VCR preceded Aza-CR and additive or synergistic when VCR followed Aza-CR. When Aza-CR was combined simultaneously with either Ara-C or ADRIA, cytotoxicity was markedly antagonistic but was additive if drugs were given sequentially. When Ara-C was given as a 24-hr infusion before Aza-CR, the resultant cell kill was antagonistic (although slightly greater than that obtained for Ara-C alone). However, antagonism was even more marked when Aza-CR was given before the 24-hr infusion of Ara-C; cell kill was less than that observed with Ara-C alone. Synergistic cytotoxicity was observed only with VCR administered after a low dose of Aza-CR. Therefore, scheduling of drugs in combination with Aza-CR may be critical in the determination of the antileukemic cytotoxic effects. (Author abstract) (18 Refs)

REVIEWS

47. ERYTHROLEUKEMIA: A STUDY OF 15 CASES AND LITERATURE REVIEW.

Roggli VL, Saleem A
(c/o Saleem) Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer; 49(1):101-108 1982

Out of a total of 185 cases of acute leukemia at our institution from 1967 to 1978, fifteen cases (8.1%) were identified as erythremic myelosis. The symptoms at presentation were often

related to anemia (10/15 cases); the presenting hemoglobin value was lower than 10.0 gm/100 ml. Nucleated red cells were present in the peripheral blood and reticulocyte response was inappropriate to the degree of anemia. Marrow biopsy showed erythroid hyperplasia with megaloblastic and dyserythropoietic features, increase in myeloblasts greater than 5% (10/15 cases), positive PAS staining of erythroid precursors (12/12 cases), and erythrophagocytosis by abnormal erythroid precursors (6/15 cases). Abnormalities were noted in monocyti c and megakaryocytic cell lines, and it was concluded that erythroleukemia is probably a stem cell disorder. Response to chemotherapy was poor with median survival of 4 months from initial diagnosis. Intracranial hemorrhage and bacterial or fungal infection were the most frequent cause of death. (Author abstract) (56 Refs)

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Diagnosis, Treatment

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DIAGNOSIS

1. BONE LESIONS IN CHRONIC MYELOGENOUS LEUKAEMIA.

Valimaki M, Vuopio P, Liewendahl K
Third Dept. Medicine, Univ. Central Hosp., SF-00290 Helsinki 29, Finland
Acta Med Scand; 210(5):403-408 1981

The incidence and site of bone lesions in 33 patients with chronic myelogenous leukemia were studied by performing bone scintigraphy and radiography. The scintigrams were abnormal in 67% and the radiographs in 29%. Increased juxtaarticular uptake of radioactivity was observed particularly in acute phase patients, whereas areas of focal uptake were detected in many chronic phase patients. Nearly all patients suffered from bone pains before the development of demonstrable osseous lesions. Hypercalcemia was found in one patient with blastic transformation and bone lysis. Two patients with exten-

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sive bone des truction were treated with vincristine, prednisone and local irradiation in spite of hematological remission. No hematological relapse has occurred in these two patients during follow-up for 12 and 41 mo, respectively. (Author abstract) (15 Refs)

2. CHARACTERISTICS OF SIMPLE DISTRIBUTIONS OF HEMATOPOIETIC BONE MARROW IN CASES OF ATYPICAL LEUKEMIA.

Miki M
First Division, Dept. Internal Medicine, Kyoto Univ. Faculty Medicine, Kyoto, Japan
Rinsho Ketsueki; 22(6):778-780 1981

Bone marrow scintigraphy using Tc-99m sulfur colloid was performed in 20 patients with aplastic anemia (APA), 6 with atypical APA (AAPA), 4 with hypoplastic leukemia (HYPL), 6 with acute myelocytic leukemia, 8 with chronic myelocytic leukemia, 1 with smouldering leukemia, and 28 with other types of leukemia. The Tc-99m sulfur colloid (10 mCi) was injected iv in the patients, and the patients' skeletons were imaged with the aid of a Hitachi Gamma-View H, 30-60 min after injection and after the patients urinated. In hematologically normal subjects, active bone marrow was visualized in the skull, sternum, vertebrae, pelvises, and heads of the humerus and femurs. In 3/20 patients with APA, 6/6 with APA, and 4/4 with HYPL, island-like spots of accumulated Tc-99m sulfur colloid were observed in the tibias and fibulas; the island-like spots were also observed in the pelvices of the patients with APA. The island-like spots in the patients with HYPL were thought to be hematopoietic sites of new clones. Similar abnormal features that were observed in both the patients with APA and those with HYPL suggested a clonal relationship between the two diseases. The Tc-99m sulfur colloid bone scintigraphy was thought to have potential as a differential diagnostic procedure for hypoplastic hematopoietic diseases, particularly HYPL. (1 Ref) (In JPN)

3. CLINICAL, HEMATOLOGICAL AND PATHOLOGICAL FEATURES OF T-CELL LEUKEMIA-LYMPHOMA IN THE NAGASAKI DISTRICT.

Kinoshita K, Kamihira S, Yamada Y, Amagasaki T, Ikeda S
Dept. Hematology, Atomic Disease Inst., Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1431-1443 1981

Surface natures of malignant cells from lymph nodes and the peripheral blood of 140 patients with non-Hodgkin's lymphoma (NHL) in the Nagasaki district were examined for T and B cell characteristics. Surprisingly, 110 cases (78.6%) were of the T-cell form on the basis of spontaneous rosette formation with sheep erythrocytes. Of the remaining cases, 17 were B-cell origin (monoclonal S-Ig positive), 9 were non T-, non B-cell and 4 cases were undetermined. Seventy-one (65.4%) of the T-cell lymphomas were of leukemic form, characterized by pleomorphism in the peripheral blood cell size, and histological appearance. However, most of the leukemic T-cells showed obvious lymphocytic differentiation, with condens ed nuclear chromatin and scant cytoplasm, although in many of the cases, lymphomatous infiltrate was dominated by either pleomorphic lymphoid cells or medium-sized cells, accompanied by occasional large multinucleated lymphoid cells. Clinically, they primarily involved middle-aged and elderly subjects, and were characterized by wide spread organ invasion (particularly to the liver, spleen and skin), susceptibility to various infections, complication of hypercalcemia and a poor prognosis. A mediastinal mass was not observed in all cases. The patients had a median survival of only 7.5 mo. On the other hand, non-leukemic T-cell lymphomas, half of which histologically showed the monotonous infiltrates of large lymphoid cells, were not different in any way from usual manifestation of malignant lymphoma with massive lymphadenopathy. These patients were generally resistant to chemotherapy and many of them died of the progression of the lymphoma within almost 1 yr. On the basis of surface marker, cell morphology, cytochemistry, and DNA synthesis of the malignant, pleomorphic T-cells, it was suggested that large lymphoid cells, namely, T-immunoblast differentiated to mature lymphocytes, resulting in a pleomorphism of the lymphoid infiltrates and leukemic manifestation. (Author abstract) (32 Refs)

4. ATYPICAL LEUKEMIA: CONCEPTS AND UNIQUE CLINICAL CHARACTERISTICS.

Takahashi I, Kohi F
Second Dept. Internal Medicine, Okayama Univ. Sch. Medicine, Okayama, Japan
Rinsho Ketsueki; 22(6):757-765 1981

Clinical and hematological characteristics of hypoplastic acute myelocytic leukemia (AML) were studied in 44 patients (32 men, 11 women, 1 unknown; 11-83 yr old) with hypoplastic AML, and the characteristics of the AML observed in the 44 patients with hypoplastic AML were compared to those observed in 168 patients with typical AML. Hypoplastic AML was defined as a condition of AML in which the patient had two or three of the following conditions: decreased marrow formation, either greater than or equal to 20% myeloblasts or greater than or equal to 40% myeloblasts + promyelocyte in bone marrow, and/or presence of Auer bodies. Frequency of hypoplastic AML was higher in patients who were 45-54 yr old than in those 34-44 yr old; hypoplastic AML occurred more often in men with AML (33/136) than in women with AML (11/76). Increased frequency of hypoplastic AML in the elderly patients as compared to the younger patients was thought to be due to the increase in the age of the population in general. A relatively long hypoplastic preleukemic condition in patients was thought to be correlated to hypoplastic AML. Fever, bleeding tendencies, organomegaly, pancytopenic with relative lymphocytosis and lack of or low percentage of leukemic cells in peripheral blood were characteristic of hypoplastic AML; low numbers of leukemic cells were not a lways observed in the bone marrow of the patients with hypoplastic AML, and presence of relatively increased numbers of RBC and Type III sideroblasts was thought to be an important hematological finding. Smouldering acute leukemia was also thought to be somehow related to hypoplastic AML. (10 Refs) (In JPN)

5. DISTRIBUTION OF 159 CASES OF ACUTE NON-LYMPHOBLASTIC LEUKEMIA (ANLL) ACCORDING TO THE FAB CLASSIFICATION, AND PROGNOSTIC CORRELATIONS.

Sanz MA, Amigo V, Gomis F, Perez Sirvent ML, Besalduch J, Rafecas J, Martinez J, Marty ML
Servicio de Hematologia y Hemoterapia, Ciudad Sanitaria de la Seguridad Social 'La Fe' de Valencia, Avda Campanar, 21, Valencia-9, Spain
Sangre (Barc); 26(5C):1019-1025 1981

One-hundred and fifty-nine ANLL patients diagnosed along a 12 yr period were reviewed. Cytological diagnosis was established in double-blind fashion by three observers applying the FAB classification criteria. The final diagnosis was reached when at least two observers coincided. The distribution, accor-

dances, and discordances in diagnosis were analyzed in order to assess the FAB classification reproducibility. Age, sex, peripheral blood counts, cellularity, mitotic index, eosinophilia, and presence of 'hand-mirror' cells were assessed in every case in an attempt to correlate such features with the classification subtypes. In the last 38 patients, who had received homogenous treatment, the rate of complete remissions, the remission duration, and the survival with respect to cell-type (ie, myeloblastic M1-M2, or monoblastic M4-M5) were also examined, no statistically significant difference being appreciated. (Author abstract) (10 Refs) (In SPA)

6. CLINICAL FEATURES OF ADULT T-CELL LEUKEMIA IN KAGOSHIMA, THE SOUTHERNMOST DISTRICT IN JAPAN - COMPARISON WITH T-CELL LYMPHOMA.

Nomura K, Matsumoto M
Second Dept. Internal Medicine, Kagoshima Univ., Kagoshima, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1444-1457 1982

Clinical features of 46 cases of ATL were investigated in comparison with those of T-lymphoma. The mean age of ATL patients was 58, with a 1.3:1 male to female ratio. Seasonal distribution showed a high frequency from May to September. Major findings of ATL were highly leukemic changes of convoluted lymphocytes, enlargement of the liver and the spleen, skin manifestation, slight or no lymphadenopathy and frequent hypercalcemia. Noticeable complications of serious pulmonary lesions and prior generalized dermatomycosis were observed in several cases. More remarkable findings of physical or laboratory examinations and complications were observed in ATL than in T-lymphoma, but no differences in survival. (Author abstract) (27 Refs)

7. AUTOMATED CYTOCHEMISTRY IN THE PREDICTION OF REMISSION FOLLOWING CHEMOTHERAPY OF PATIENTS WITH DE NOVO ACUTE MYELOBLASTIC LEUKEMIA.

Winkel P, Olesen T, Nissen NI
Dept. Clinical Chemistry, Finseninstitute, Strandboulevarden 49, Copenhagen, 2100, Denmark
Am J Clin Pathol; 77(1):50-53 1982

In seven patients with de novo acute myeloblastic leukemia, the concentration of large unstained cells (LUC) in peripheral blood and the ratio between this quantity and the concentration of lymphocytes (LUC/LYMPH) were measured at short intervals during each patient's clinical course. An automated differential analyzer (the Hemalog-D) was used. Both quantities were significantly higher 12 days after the institution of daunomycin and cytosine arabinoside chemotherapy (between first and second treatment series when all patients were pancytopenic) in three of the patients who did not achieve remission (mean LUC = 59 cells/ul, mean LUC/LYMPH = 13.9), as compared with four of the patients who went into remission following two series of chemotherapy (mean LUC = 16 cells/ul, mean LUC/LYMPH = 3.11). (Author abstract) (5 Refs)

8. CLINICAL PATHOLOGY OF ADULT T CELL LEUKEMIA.

Hanaoka M
Dept. Pathology, Inst. Virus Res., Kyoto Univ., Kyoto, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1420-1430 1981

There are three main categories of mature T (T2) cell leukemia, ie monomorphic leukemia, Sezary syndrome and adult T cell leukemia (ATL). ATL which is different from Sezary syndrome in clinical features is characterized by the appearance of neoplastic cells with a peculiar nucleus polymorphism. ATL showed a poor prognosis of 4.7 mo in the median survival time in comparison to other types of T2 cell leukemia. Lymph nodes of patients with ATL were histologically diffuse lymphoma, pleomorphic type (PML) in 72% of the total cases observed. This histologic feature was similar to that of non-leukemic PML for which the term 'adult T cell leukemia/lymphoma (ATLL)' has been proposed. PML in biopsy lymph nodes accounted for 10-12% of the Hodgkin's lymphomas observed both in Kyoto University Hospital during the 10 yr period from 1971 to 1980 and a nationwide survey. The high incidence of ATLL resulted in a geographically eccentric distribution of T cell malignancies in southwestern Japan. (Author abstract) (31 Refs)

9. INITIATION OF BLAST CRISIS OF CHRONIC MYELOID LEUKAEMIA IN EXTRAMEDULLARY SITES.

Blackshaw AJ, Sutcliffe SB, Saary J d
(c/o Sutcliffe), Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Clin Oncol; 7(4):311-324 1981

Transformation of chronic myeloid leukemia (CML) into a blast cell proliferation may occur in peripheral lymph nodes or other extramedullary sites (myeloblastic sarcoma). Occasionally transformation in such sites precedes the conventional blast crisis seen in the bone marrow and peripheral blood. Four cases of myeloblastic change in lymph nodes preceding marrow blast crisis are presented h ere, and a further 20 cases of similar extramedullary blast crisis are reviewed from the literature. The differential diagnosis of myeloblastic sarcoma producing lymphadenopathy in patients with CML is discussed, both in terms of the clinical implications and the histological differentiation from other lymph node disease. (Author abstract) (41 Refs)

10. INTRACELLULAR 'LABYRINTHS' IN ACUTE LEUKAEMIA. DO THEY INDICATE THE MATURATIONAL ABILITY OF LEUKAEMIC CELLS?

Lelkes G, Lelkes G, Natonek K, Hollan SR
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Haematologia (Budap); 14(3):293-306 1981

Bone marrow cells of 13 patients with acute leukemia were examined for intracellular labyrinths and the ultrastructure of the labyrinths was described. Labyrinths were present in cells from seven of eight patients with acute myeloid leukemia (AML) but not in cells from three with acute lymphoid leukemia, one with acute plasma cell leukemia, or one with acute undifferentiated leukemia. In patients with preleukemia, labyrinths were found in cells at all stages of differentiation, from myeloblasts to mature polymorphonuclear granulocytes (PMN). Populations of normal and abnormal PMN occurred in one patient with AML; labyrinths were present only in the abnormal population. In severe AML, where no mature cells were observed in bone marrow, only precursors arising from myeloid stem cells contained labyrinths. Results suggest that labyrinths may be of diagnostic value in leukemia. Their presence in mature granulocytes suggests that in vivo maturation of leukemia precursors takes place in certain cases of AML and preleukemia. (17 Refs)

11. ULTRASTRUCTURE OF ADULT T-CELL LEUKEMIA/ LYMPHOMA.

Eimoto T, Mitsui T, Kikuchi M
Dept. Pathology, Fukuoka Univ. Sch. Medicine, Nanakuma 34, Nishi-ku, Fukuoka, 814-01, Japan
Virchows Arch [Cell Pathol]; 38(2):189-208 1981

Eighteen cases of adult T-cell leukemia/lymphoma (ATLL) in Japan were analyzed by electron microscopy and compared with 5 cases of B-lymphoma and well-established groups of T-lymphomas (4 cases of T-lymphoblastic lymphoma and 2 cases of Sezary syndrome). Five hundred cells in each case, categorized ultrastructurally as to the cellular size and nuclear shape, showed an essentially pleomorphic cellular distribution in ATLL in remarkable contrast with the monomorphism of B-'histiocytic', B-well-differentiated lymphocytic, and T-lymphoblastic lymphomas. Some B-lymphomas and Sezary syndrome also showed pleomorphism. Cases of ATLL were classified according to the predominant cells and degree of nuclear irregularity, which delineated a spectrum of node-based, peripheral T-cell neoplasms probably encompassing T-immunoblastic sarcoma, T-zone lymphoma, as well as multilobated T-cell lymphoma. The characteristic fine structure of ATLL, in comparison with that of B-lymphomas, included slight to marked nuclear irregularity with convoluted-shape predominance, a speckled chromatin pattern of the large cells, prominent lysosomes, and glycogen accumulation in addition to the difference in cellular distribution. Although T-lymphoblastic lymphoma and Sezary syndrome shared some of these features, the ultrastructural differentiation of ATLL from them seems to be possible. (Author abstract) (31 Refs)

12. TRANSLOCATION 4;11 IN ACUTE LYMPHOBLASTIC LEUKEMIA: CLINICAL CHARACTERISTICS AND PROGNOSTIC SIGNIFICANCE.

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Blood; 59(1):96-99 1982

Banded bone marrow chromosome analyses have been done on 83 unselected patients with acute lymphoblastic leukemia (ALL). Seven patients, all with non-T, non-B ALL, had a translocation involving the long arms of chromosomes 4 and 11. Five of these patients, four children and one adult, were first studied at diagnosis, and the t(4;11) (q21;q23) was the only karyotypic abnormality. All five presented with a marked leukocytosis (greater than 150 x 10(9)/liter). Four of these five patients achieved a complete remission following the same intensive treatment regimen; however, remission duration and survival were very short (medians 2.5 and 8 mo respectively). The fifth patient is currently receiving induction chemotherapy. The remaining two patients, both adults, were studied in relapse only, and had other karyotypic abnormalities in addition to the t(4;11). One of these relapse patients was a female whose clinical presentation and course were similar to those above. The last patient was a male who presented with a leukocyte count of 7 x 10(9)/liter and maintained an initial complete remission for 37 mo. Our data suggest that patients who have a t(4;11) (q21;q23) at the time of diagnosis of ALL have a poor prognosis with conventional therapy and require a new therapeutic approach. (Author abstract) (11 Refs)

13. FEATURES OF CHROMOSOMAL ABNORMALITIES IN ATYPICAL LEUKEMIA.

Tagawa M, Tomonaga Y
Dept. Hematology, Atomic Disease Inst., Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Rinsho Ketsueki; 22(6):789-791 1981

Bone marrow cells from 13 patients with atypical leukemia were studied cytogenetically using the banding technic. Chromosomal abnormalities were observed in three patients: missing Y, t(8;21), or 5p-with multiple change. Abnormal and normal diploid cells coexisted in all three patients. Cellular aging might have resulted in the loss of the Y chromosome. Clonal evolution of the karyotype could not be seen in 11 patients for whom serial cytogenetic analyses were obtained. (6 Refs) (In JPN)

14. CYTOGENETIC STUDIES IN ADULT ACUTE LEUKEMIAS.

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Dept. Genetics and Endocrinology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(4):293-302 1981

Thirty-six patients with acute leukemia (31 with AML, 5 with ALL) were classified by FAB criteria, and their bone marrow cells were analyzed cytogenetically with G-banding. Chromosomal abnormalities were found in 16 patients (44%). The most common abnormality was an 8;21 translocation, accounting for 19.4% of all AML patients, that was restricted to patients with M2. In 29 treated AML patients, those with an 8;21 translocation [t(8;21) patients] showed a higher complete remission rate (83%) and a longer median survival (10.7 mo) than did other patients with AML; patients with only abnormal metaphases (AA patients) had the lowest complete remission rate (33%) and shortest median survival (2.7 mo). There was no difference in the remission rate and the survival between patients with only normal metaphases (N patients) and patients with abnormal metaphases (A patients). Three out of five patients with ALL had karyotypic abnormalities; the Philadelphia (Ph1) chromosome was found in one case. (Author abstract) (31 Refs)

15. 9;22;15 COMPLEX TRANSLOCATION IN PH1 CHROMOSOME POSITIVE CML REVEALED BY GIEMSA-11 PROCEDURE IN APPARENT LYMPHOID CELLS OF BLASTIC CRISIS.

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Cancer Genet Cytogenet; 4(4):283-292 1981

A Ph1 chromosome positive chronic myeloid leukemia patient whose chronic phase lasted 7.5 yr experienced a blastic transformation originating in the spleen. The spleen was infiltrated with undifferentiated blast cells that on cytogenetic analysis had a hyperdiploid karyotype and were Ph1 chromosome positive. The blast cells were negative for PAS, peroxidase, Sudan black and esterase stains. They were non-T, non-B with TdT activity. Remission was achieved in response to prednisone, vincristine, and adriamycin. Ph1 positive cells were present with cells responding to PHA stimulation throughout the course of the disease. A Giemsa-11 staining procedure made possible the ascertainment of a No 9 translocation chromosome in blastic crisis cells that had also been present in Ph1 chromosome positive cells early in the disease. The presence of this translocation initially in myeloid cells and subsequently in ap-

parent lymphoid cell types suggests the origin of this patient's leukemia as a pluripotential stem cell. (Author abstract) (16 Refs)

16. ATYPICAL LEUKEMIA: WHY DO THEY BECOME ATYPICAL? (PATHOLOGICAL ANALYSIS) - FROM THE PERSPECTIVE OF HEMOPOIETIC CELLS.

Saito Y, Uzuka Y
Third Dept. Internal Medicine, Tohoku Univ. Sch. Medicine, Sendai, Japan
Rinsho Ketsueki; 22(6):781-788 1981

Kinetics of hemopoietic cells from the bone marrow of 10 patients (8 men, 2 women; 33-76 yr old) with atypical leukemia (ATL; 6 cases of smouldering acute leukemia, 4 of hypoplastic leukemia) were studied with the aid of culturing. Bone marrow from the patients was cultured with conventional agar culture method using phytohemagglutinin-leukocytic meningitis (PHA-LCM) from peripheral WBC of normal subjects in order to study colony forming unit-colony (CFU-C). Stage colony-stimulating factor (CSF) was measured with 3H-thymidine suicide experiments. In order to investigate the patients' colony stimulating activity (CSA), PHA(+)LCM or PHA(-)LCM from peripheral blood of the patients was added to marrow cells from normal subjects, CFU-C of the normal marrow cells were estimated, and CSF activity was measured. Cytological, cytochemical, and immunological examination of all colonies was performed as well. Normal colony formation was observed in 2/10 cases, markedly decreased colony formation was observed in 7/10, and no colony formation was observed in 1/10. High levels of cluster colonies were observed in 2/10. Suicide indices for the marrow CFU-C of the patients (1-25%) was comparatively lower than those of the normal subjects (23.8-34.2%). CSA was within normal values for 1/10 patients and was markedly decreased in all of the others. Decreased CSA, CFU-C, and suicide indices suggested impaired proliferation and differentiation of pluripotent stem cells. These in vitro culture methods may have some effective application to diagnosis, treatment, and determination of the causes of atypical leukemia. (24 Refs) (In JPN)

17. ATYPICAL LEUKEMIA: CLINICOPATHOLOGICAL ANALYSIS FROM CYTOKINETIC ASPECTS - CYTOKINETIC CHARACTERISTICS OF BLAST CELLS IN REFRACTORY ANEMIA WITH AN EXCESS OF MYELOBLASTS.

Tsuchiya J, Shinonome S, Takakuwa M, Murakami H, Miyao S, Shimano S, Suda T, Omine M, Maekawa T
Third Dept. Internal Medicine, Gunma Univ. Sch. Medicine, Maebashi, Japan
Rinsho Ketsueki; 22(6):768-777 1981

Blast cell cytokinetics were investigated in blast cells in 19 patients (14 men, 5 women; 12-81 yr old) who had refractory anemia with an excess of myeloblasts (RAEM). Diagnostic criteria of RAEM included chronic anemia, leukopenia and thrombocytopenia, moderate and static excess of myeloblasts and promyelocyte in the bone marrow, and stability of myelograms for greater than 3 mo. Cases of RAEM were divided into two groups (A and B) based on myeloblast and promyelocyte percentages of total marrow nucleated cells (Group A, less than or equal to 20%; Group B, greater than 20%). Cytokinetic data of the blast cells were compared with those of blast cells in 36 patients with overt acute myelocytic leukemia (AML). Proportions of abnormal circulating neutrophils that lacked myeloperoxidase and/or naphthol-ASD-chloroacetate-esterase activities were observed to be significantly (p less than 0.01) increased in blast cells of patients with of RAEM compared to those of AML; this suggested that the small changes observed in the blast ratios in patients with RAEM may be due to relatively high rates of differentiation and maturation of the blast cells. Compared to serum lysozyme levels in healthy control subjects (5.5 +-0.3 ug/ml), those in the patients with RAEM (16.7 +-3.8 ug/ml) were significantly increased, suggesting significantly ineffective granulopoiesis. The 3H-TdR labeling-index (LI) value of myeloblasts and promyelocytes in bone marrow of the patients with RAEM was in between the values of labeling-indices of the healthy control subjects and the patients with AML; the LI of Group A was higher than that of Group B, and the LI of Group B (9.1 +-2.3%) was close to that of the patients with AML (7.1 +-0.6%), suggesting that Group A RAEM may need to be put in a different category than Group B RAEM. (30 Refs) (In JPN)

18. CHANGES IN LYMPHOCYTES AS AN EARLY SIGN OF RELAPSE IN ADULT ACUTE LEUKEMIA.

Kawamura S, Abe I, Saitoh A, Yamaya T, Tsuchida S, Chiba Y, Yoshida Y
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Tohoku J Exp Med; 135(3):237-245 1981

Laboratory tests were administered to 23 patients (17 males, 6 females; 18-53 yr old) during the remission phase of leukemia (15 acute myelocytic; 8 acute lymphocytic) until relapse occurred, and an attempt was made to correlate test result changes with the onset of relapse. Blood examinations consisted of total protein, albumin/globulin ratio, lactate dehydrogenase activity, zinc sulfate test, erythrocyte sedimentation rate, C-reactive protein, and immunoglobulin levels (IgG, IgA, IgM), determined once during remission and once during relapse. Red cell counts, white cell counts with differential hemoglobin levels, platelet counts, and reticulocyte counts in the peripheral blood were done every 2 wk after remission until relapse. T-cells and B-cells were counted by E-rosette and EAC-rosette formation; blastogenesis of lymphocytes was measured by 3H-uridine incorporation after stimulation with phytohemagglutinin-P. Bone marrow cells aspirated from the sternum and ilium were cultured. Neither laboratory blood tests nor blood counts showed significant changes in association with relapse. Bone marrow cultures did not show significant differences either, but percentages of both T- and B-cells had decreased markedly at the time of relapse. A decrease in T- and B-lymphocytes or an increase in peripheral blood lymphocytes greater than 40-50% during maintenance therapy indicates the need for immediate bone marrow puncture. (15 Refs)

19. II-EVALUATION OF THE PROGNOSTIC VALUE OF THE PLASMA LYSOZYME LEVELS IN LEUKEMIA PATIENT DURING THERAPY.

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Indian J Cancer; 18(4):262-267 1981

The prognostic value of plasma lysozyme during management of leukemia patients and the correlation of plasma lysozyme levels with those of leukocytes in these patients were investigated. Plasma was obtained from 53 normal subjects and 14 patients with various types of leukemia. These patients were examined at various stages of their disease. A good correlation between WBC count and plasma lysozyme was observed in 8/14 patients. The case histories of three representative patients in whom such a correlation was observed are reported. Plasma

concentrations of lysozyme were found to be high before treatment, fell to normal levels during remission, or levels diminished following partial response to treatment and rise during resistance to treatment. Pre-treatment elevated levels of the enzyme in two patients were associated with high leukocyte counts. With the diminution of WBC count, enzyme levels decreased. In three cases where the WBC counts were initially high, lysozyme levels were either elevated or on the upper limit of normal. Results indicate that plasma lysozyme has limited usefulness as a marker in the management of leukemia. (10 Refs)

20. CAMP RECEPTOR PROTEINS AND PROTEIN KINASES IN HUMAN LYMPHOCYTES: FUNDAMENTAL ALTERATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS.

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Eur J Biochem; 120(3):585-592 1981

To study the significance of cAMP receptor proteins and protein kinase activities in tumor dys-differentiation, peripheral blood lymphocytes from normal donors and from patients with chronic lymphocytic leukemia were isolated by Percoll gradient centrifugation, and analyzed. Both normal and tumor lymphocyte populations were devoid of cell proliferation. Normal human lymphocytes contained about equal activities of histone kinase and 'casein kinase'. The tumor lymphocytes, however, exhibited drastically reduced values of all three protein kinase activities, the most pronounced decrease being observed with the 'casein kinase'. Total high-affinity cAMP-binding sites (= regulatory subunits R of cAMP-dependent protein kinases Type I and II) in leukemic lymphocytes were also strongly reduced. The findings in lymphocytes of chronic lymphocytic leukemia cannot be explained by the fact that they are B-type lymphocytes. Control experiments revealed that normal B cells do not differ significantly from total blood lymphocytes with respect to the parameters mentioned above. Biochemical correlates of the dys-differentiated status of these non-proliferating cells from patients with chronic lymphocytic leukemia, then, are represented by reduced levels of protein kinases, of basal cAMP as well as by changes in the R-protein pattern. The data indicate that both protein kinases Type I and Type II may relate to the state of differentiation, independently from cell proliferation. (57 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

21. RELATIONSHIP BETWEEN HLA-DR5 ANTIGEN AND SURVIVAL OF PATIENTS WITH ACUTE CHILDHOOD LEUKEMIA.

Revesz T, Benczur M, Gyodi E, Petranyi GGy, Schuler D
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Orv Hetil; 122(45):2765-2766 1981

Relationships between HLA antigens and survival were studied in 46 children in remission from acute lymphocytic leukemia (ALL). Ten of the 46 patients were still being treated at the time of the investigation. The occurrence of the HLA-A, B and C locus antigens did not differ significantly from that in healthy controls. Among the D locus antigens, which play an important role in immune reactivity, the frequency of the HLA-DR5 antigen was somewhat higher among the patients (32% in 15/46 patients, including 11/28 girls and 4/18 boys) than in the general population (20.2%). The incidence of HLA-DR5 antigen was significantly higher among the patients who have been alive for more than 3 yr (15/38 patients: 11/27 girls and 4/11 boys) than in those who survived less than 3 yr (1/8 patients). The av length of remission and av survival of the HLA-DR5-positive patients were 77.0 +-9.0 mo and 78.9 +-9.0 mo, respectively, and those of the HLA-DR5-negative patients were 54.0 +-4.4 mo and 58.4 +-4.2 mo, respectively. No relationships were found between the occurrence of HLA-DR5 antigen, on one hand, and the initial leukocyte and thrombocyte counts, initial hemoglobin level, and age at diagnosis, on the other hand. The findings indicate the prognostic significance of HLA-DR5 antigen. (10 Refs) (In HUN)

22. BIOCHEMICAL AND IMMUNOLOGIC HETEROGENEITY OF IA GLYCOPROTEINS ISOLATED FROM A CHRONIC LYMPHOCYTIC LEUKEMIA.

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J Immunol; 128(1):217-223 1982

Ia glycoproteins have been isolated from human chronic lymphocytic leukemic cells (CLL) by Lens culinaris chromatography and by filtration on ACA-34 Ultrogel. Ia antigenic activity, measured by inhibition of the cellular radioimmunoassay, was separated by gel filtration into two fractions, Peak I and Peak II. Monoclonal antibodies, produced against Peak II glycoproteins, appear to recognize different antigenic determinants of Ia molecules. Monoclonal antibody 18a4 reacted with Ia molecules of Peaks I and II, whereas monoclonal antibodies 18c2 and 18d5 reacted almost exclusively with Peak II molecules both in the cellular radioimmunoassay and by immunoprecipitation. In addition to antigenic differences, minor variations in the apparent mol wt of the Ia polypeptide chains were observed between Peaks I and II. These results indicate the existence of antigenically distinct subsets of Ia molecules that are separable by gel filtration. (Author abstract) (50 Refs)

23. CELL MARKERS IN HAIRY CELL LEUKEMIA STUDIED IN CELLS FROM 51 PATIENTS.

Jansen J, Schuit HR, Meijer CJ, Van Nieuwkoop JA, Hijmans W
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Blood; 59(1):52-60 1982

To determine the maturation arrest of the neoplastic cells of hairy-cell leukemia (HCL) and the spectrum of the surface markers on these cells, a series of 51 patients with this disease was studied. The cells of all but two of the patients showed monoclonal surface Ig with respect to light chains. In about one-third of the cases, only gamma heavy chain determinants were present on the cells; the majority carried multiple heavy chain determinants as documented by the application of different fluorochromes. Two patients each showed two different clones of cells, both of the same light chain type. In one of these two patients, two paraproteins were present in the serum. Intracytoplasmic Ig was found in only 4 of 39 cases, in all instances being IgM. All cases studied concerned cells with FcIgG receptors; however, the density of this receptor varied. FcIgM receptors also showed a spectrum of density, with

some cases showing very few FcIgM-positive cells. Receptors for C3 were not observed on the hairy cells. Serum immunoglobulin levels were normal or increased. Paraproteins were found in the sera of 4 of 38 patients. These data suggest that HCL is a neoplasm of B lymphocytes. The neoplastic cells are probably arrested at a more mature stage than the cells of chronic lymphocytic leukemia. The multiple isotypes on the cells indicate a block at the 'switch' phase from the small mu-carrying lymphocyte to the larger Ig-producing lymphocyte or plasma cell. (Author abstract) (42 Refs)

24. THE NATURE OF THE IMMUNOGLOBULIN G ON THE SURFACE OF B LYMPHOCYTES IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Stevenson FK, Hamblin TJ, Stevenson GT
Lymphoma Res. Unit, Tenovus Res. Lab., General Hosp., Southampton, England
J Exp Med; 154(6):1965-1969 1981

Anti-idiotypic antibody was raised against the surface IgM on neoplastic B lymphocytes of five patients with chronic lymphocytic leukemia. Radioimmunoassay of cell lysates indicated that Mu was the predominant heavy chain class for all five patients. This included both surface membrane and intracellular IgM. The levels of IgD and IgG found in lysates were low, with IgG exceeding IgD for all patients. Passage of cell lysates through specific anti-idiotypic immunosorbents resulted in almost complete remov al of IgM in all five patients; passage of lysates through control immunosorbents resulted in recovery of 79-123%. Similar results were obtained with IgD, with larger errors due to the small amounts of IgD present. For IgG, however, 81-100% passed through the anti-idiotypic column and 71-100% passed through the control, demonstrating the non-idiotypic nature of the IgG. The majority of all three immunoglobulin (Ig) idiotypes were not retarded when the lysate from the cells of one patient was passed through an immunosorbent carrying anti-idiotype directed against another patient's lymphocytes of the same surface Ig isotype. Thus the IgG frequently found associated with lymphocytes at this stage of differentiation is likely to be extrinsic in origin. (11 Refs)

25. CORRELATION OF CIRCULATING IMMUNE COMPLEXES AND DISEASE STATUS IN PATIENTS WITH LEUKAEMIA.

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Clin Exp Immunol; 43(1):46-53 1981

The occurrence of soluble immune complexes (IC) was investigated in 177 serum samples from 92 patients with various leukemias using the Raji cell immunoassay. In general, patients with myeloproliferative diseases had a higher incidence and higher quantities of IC than did patients with lymphoproliferative disorders. Elevated levels of IC were found in the sera of patients as follows: 17% with chronic lymphocytic leukemia (mean value of 13.1 ug/ml), 67% with acute lymphocytic leukemia (54.1 ug/ml), 65% with chronic myelocytic leukemia (86.7 ug/ml), 70% with acute myelocytic leukemia (202.5 ug/ml) and 56% with acute myelomonocytic leukemia (41.9 ug/ml). Patients in terminal blastic crisis of chronic myelocytic leukemia had the highest levels, with a mean level of 1,364.1 ug/ml. Serial samples were obtained, as available, from individual patients during the course of the disease in an attempt to relate severity with the incidence and quantity of IC. No significant correlation could be made between the occurrence or levels of IC and the presence or absence of systemic symptoms. Similarly, no correlations could be made between levels of IC and hematological parameters, infection, or therapy. However, the data does indicate a positive relationship between the levels of IC and the progressive state of the leukemia, especially, the myelocytic leukemias. (Author abstract) (27 Refs)

26. T-CELL GROWTH FACTOR-MEDIATED PROLIFERATION OF LYMPHOCYTES FROM A T-CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENT LACKING MITOGEN AND ALLOANTIGEN RESPONSIVENESS.

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Div. Immunology, The Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Clin Exp Immunol; 43(2):302-310 1981

Peripheral blood lymphocytes (PBL) of chronic lymphocytic leukemia of T cell ori gin (T-CLL), which were unresponsive to mitogens and had negligible stimulator and responder capacities in mixed lymphocyte cultures (MLC), were induced to proliferate by human T cell growth factors (TCGF). Long-term T-CLL PBL cultures were obtained in the presence of TCGF. T-CLL PBL obtained from a female patient (30 yr old) showed no 3H-thymidine (3HTdR) incorporation when stimulated with various concentrations of phytohemagglutinin (PHA), Concanavalin A, or pokeweed mitogen. The T-CLL PBL exhibited greatly reduced responder and inducer capacities (12% and 14% that of normal sheep RBC rosette-forming cells, respectively). TCGF-1 had the strongest growth-promoting activity and was used as a standard (1.0 growth-promoting unit). TCGF-1,-2, and-3 contained 0.52, 0.29, and 0.33 growth-promoting units, respectively. PHA stimulated proliferation of T-CLL cells in the presence of TCGF-1. Both TCGF-3 and-4 also induced and maintained T-CLL PBL proliferation in the presence of PHA, but at considerably lower rates than those produced in the presence of TCGF-1 and-2. In MLC, addition of TCGF-4 resulted in a four-fold increase in 3H-TdR incorporation in T-CLL PBL after stimulation with lymphocytes from a normal donor (C). Lymphocytes from donor C showed an 80-fold increase in 3H-TdR incorporation when cultured with T-CLL PBL in the presence of TCGF-4. The results indicated that the lack of response to mitogens and alloantigens of the T-CLL PBL can be attributed to the failure of these cells to produce TCGF upon activation. (36 Refs)

27. LYSIS OF FRESH HUMAN B-LYMPHOCYTE-DERIVED LEUKEMIA CELLS BY INTERFERON-ACTIVATED NATURAL KILLER (NK) CELLS.

Pattengale PK, Gidlund M, Nilsson K, Sundstrom C, Sallstrom J, Simonsson B, Wigzell H
Dept. Pathology, Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Int J Cancer; 29(1):1-7 1982

Fresh neoplasic B cells from 14 untreated patients with naturally occurring B-cell leukemias were found to be susceptible to lysis by human natural killer (NK) cells. The observed lysis of the fresh, non-cultured, neoplastic B cells was mediated by a population of interferon-augmentable, FcR-positive, non-adherent lymphoid cells, which were also able to kill the 'standard' NK target K562. A further finding was the correlation of NK susceptibility with disease available in 11 patients with chronic lymphocytic (CLL) and one patient with lymphosarcoma cell leukemia (LSCL). Enriched neoplastic B cells from seven untreated patients with non-progressive CLL, whose disease ac-

tivity was stable throughout the 6 mo period of study, exhibited persistent and essentially unchanged NK susceptibility profiles. In contrast, four untreated patients with progressive CLL also had a measurable fraction of NK-susceptible, neoplastic targets, but these cells subsequently disappeared after successful cytoreductive therapy, and later re-em erged when these patients again developed progressive disease. Furthermore, one patient with LSCL was found to have persistent, measurable NK susceptibility in his tumor-enriched fraction after unsuccessful cytoreductive therapy. An additional finding in the peripheral blood of patients with chronic B-cell leukemias was the presence of significantly lower NK effector-cell activity against K562 as compared to normal donor peripheral blood lymphocytes (PBLs). The implications of these findings are discussed. (Author abstract) (25 Refs)

28. IMMUNOLOGIC PARAMETERS OF CHILDREN WITH ACUTE LEUKOSIS AFTER CESSATION OF POLYCHEMOTHERAPY UNDER REPEATED IMMUNOSTIMULATION WITH INTRADERMAL B.C.G.

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Arch Geschwulstforsch; 52(2):123-128 1982

Immunologic parameters were measured in children with acute leukosis during immunostimulation with BCG after cessation of polychemotherapy. Fourteen patients, including 11 with acute lymphoblastic leukemia (ALL) and 3 with acute myeloblastic leukemia (AML) began immunostimulant therapy 6 wk after cessation of a 3-yr course of intensive polychemotherapy. BCG (0.05 ml) was injected id 2x/yr up to 5 yr and once/yr thereafter. BCG vaccination produced significant increases in peripheral-blood counts of lymphocytes (4,466 x 10(9)/liter before BCG vaccination to 7,240 x 10(9)/liter 6 wk after the third vaccination) and cells forming E-rosettes (48.5 +-21.1% before BCG treatment to 53.2 +-13.0% 6 wk after the third vaccination). Three out of 24 skin tests showed positive tuberculin reaction. A control group of patients with AML who received polychemotherapy but no BCG treatments showed no such increases. No relapse occurred in 14 patients receiving BCG during 1-3 yr observation. Among controls 19/30 were alive and 15/30 were in stable remission after an av 4 yr. Results suggest beneficial effects of BCG vaccination for patients with ALL or AML, but the patient sample was too small too draw definite conclusions. (11 Refs)

CHEMOTHERAPY

29. INTERMEDIATE DOSE METHOTREXATE (IDM) IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA IN NORWAY. REPORT ON A NATIONAL TREATMENT PROGRAM.

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Haematologia (Budap); 14(3):257-263 1981

Results of intermediate-dose methotrexate (MTX) with leukovorin rescue as treatment in hospitalized patients following induction therapy were investigated in 95 children with acute lymphocytic leukemia. Induction therapy consisted of vincristine and steroids followed by L-asparaginase for 10 days. After complete remission had been achieved three iv infusions of MTX were given at 3-wk interva ls, with one-third of the dose given as a bolus. A single dose of leukovorin, 12 mg/square meter (m2), was given 24 hr after the iv MTX. At the start of induction therapy, each patient received intrathecal MTX (12 mg/m2); all but six patients received a total of eight such doses. During the maintenance phase, patients received 6-mercaptopurine, vincristine, prednisone, and MTX. During a median follow-up period of 36 mo, only 15 relapses occurred. Twelve patients, of whom 5 were in continuous complete remission, died during the follow-up period. According to probability curves, approx two-thirds of the patients were still in remission at 57 mo. Incidences of CNS leukemia and combined systemic CNS leukemia were low (5 cases diagnosed during the study). Testicular involvement was not present in any of the 58 boys studied, suggesting that routine testicular biopsy is unnecessary when using this protocol. (6 Refs)

SURGERY

30. SPLENECTOMY FOR HAIRY CELL LEUKAEMIA.

Ingoldby CJ, Ackroyd N, Catovsky D, Spencer J
Dept. Surgery, Royal Postgraduate Medical Sch., Hammersmith Hosp., DuCane Road, London W12 0HS, England
Clin Oncol; 7(4):325-331 1981

Hairy cell leukemia is a rare disorder, in which splenectomy may be beneficial. The results of surgery in 21 patients are reported. Splenectomy was normally reserved for patients with deteriorating blood counts. Thirteen patients showed a complete hematological response after splenectomy, 5 had a partial response, and 3 did not respond. Ten of the complete responders survived more than 5 yr, as did 3 of the partial responders. None of the non-responders lived 2 yr. Platelet infusions were found valuable, and bleeding during surgery was not a major problem. Post-operative infections were common and antibiotic prophylaxis is advised. The good response to splenectomy emphasizes the importance of accurate diagnosis of this unusual condition. (Author abstract) (11 Refs)

MULTIMODAL THERAPY

31. RESULTS OF INTENSIVE TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA.

Clarkson B
Memorial Sloan-Kettering Cancer Center, New York, NY
Nippon Ketsueki Gakkai Zasshi; 44(7):1263-1276 1981

Results of some cytokinetic studies in chronic myelogenous leukemia (CML) and recent attempts to alter the natural course of the disease are summarized. Patients treated with a single large dose of splenic radiation (800 rad) responded with only minor effect, but 6 wk later the same total dose given in eight fractions over a 3-wk period caused much greater and longer lasting reduction in WBC and spleen size. Fractionated irradiation of large amounts of bone marrow were also carried out to determine if similar effects would occur. Of 37 patients with typical Philadelphia chromosome positive (Ph'+) CML who were studied, 12 had significant reduction in the proportion of cells in the marrow containing the Ph ' chromosome to less than one third of the initial values. In seven, no Ph'+ metaphases were found in the marrow. The absence of Ph'+ cells

lasted only one to several mo in most, and only two patients had sustained reduction for over 3 yr. Median survival rate of the 37 patients was 50 mo; that of non-responders was 34 mo, while survival rate of 12 responders was approx 7 yr. The L-15 protocol was completed by 28 patients: splenic irradiation or hydroxyurea to control the leukocyte and platelet count, splenectomy, and combination therapy for remission induction with daunorubicin, cytosine arabinoside by continuous infusion, and 6-thioguanine. In 12/15 responders, all of the marrow metaphases found on direct chromosome preparations were entirely Ph' negative. The remissions were only temporary. (27 Refs)

32. TREATMENT OF CHRONIC GRANULOCYTIC LEUKEMIA WITH CHEMORADIOTHERAPY AND TRANSPLANTATION OF MARROW FROM IDENTICAL TWINS.

Fefer A, Cheever MA, Greenberg PD, Appelbaum FR, Boyd CN, Bruckner CD, Kaplan HG, Ramberg R, Sanders JE, Storb R, Thomas ED
Div. Oncology, BB1025 Health Sciences, Univ. Washington, Seattle, WA, 98195
N Engl J Med; 306(2):63-68 1982

Treatment of Philadelphia (Ph)-positive chronic granulocytic leukemia (CGL) by supralethal chemoradiotherapy and marrow transplantation from an identical twin is reported. Twelve patients (13-46 yr old) in the chronic phase of CGL and 10 (11-54 yr old) in the terminal phase of CGL received 920-1000 rad of 60 Co total body irradiation in a single exposure. Bone marrow from donor iliac crests was infused in within 24 hr of irradiation. Results for patients in the chronic phase showed hematopoiesis restoration and complete clinical and cytogenic remission with disappearance of all Ph positive metaphases in all 12 patients. Marrow engraftment was detectable histologically by 2 wk after transplantation. The absolute granulocyte count rose to greater than 500 by days 12-33, counts greater than 20,000 without supporting platelet transfusions were common by days 13-32. Side effects and complications included gastrointestinal toxicity, rashes, mild liver function abnormalities, fever (greater than 38 C), viral infections, dry mouth, and amenorrhea. Eight patients remain in complete remission 21-65 mo (median greater than 30 mo) after transplanation. Six terminal phase CGL patients entered complete remission and four died 10-17 days after transplantation. Cytogenic evaluation after transplantation showed no detectable pH positive metaphases in 4 patients (3 ultimately had relapses); 3 still had Ph positive metaphases. Apparently blast crisis is delayed and survival is prolonged by twin-marrow transplantation. (30 Refs)

33. MENINGOSIS PROPHYLAXIS WITH INTRATHECAL 198AU-COLLOID AND METHOTREXATE IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA.

Metz O, Stoll W, Plenert W
Dept. Pediatrics, Carl-Zeiss-Stiftung, Kochstrasse 2, 6900 Jena, E. Germany
Cancer; 49(2):224-228 1982

Since 1972, telecobalt irradiation plus intrathecal methotrexate (ITMTX) has been successfully replaced in Jena by intrathecal colloidal radioactive gold (198Au) plus ITMTX for meningosis prophylaxis in leukemia. Seventy-three children with acute lymphocytic leukemia (ALL) were given 1.24-4.89 mCi (45.8-181 MBq) of colloidal 198AU IT after successful initiation of remission. During cytostatic therapy, the following relapses occurred: meningosis leukemica, five patients (6.8%); bone-marrow relapse and meningosis leukemica, one patient; and bone-marrow relapse, 20 patients (27.4%). In 18 children, combination chemotherapy was terminated after 2 1/2 or 3 yr of treatment. After that time, one meningeal relapse and six bone-marrow relapses occurred. Within the first 24 hr after application of radioactive gold, headaches, vomiting, and fever occurred in less than 10% of the children. An apathy syndrome, leukencephalopathy, or severe infections, were not observed in a single case. Radioactive gold spreads in the subarachnoid space and is phagocytized by the arachnbidea. The tumoricidal effect extends selectively over the space of distribution of the latent meningosis leukemica. The cerebral parenchyma remains unaffected by radiation. Thus, radioactive gold may be preferable to telecobalt irradiation in preventing central nervous system leukemia. (Author abstract) (33 Refs)

34. SANCTUARY THERAPY: A RANDOMIZED TRIAL OF 724 CHILDREN WITH PREVIOUSLY UNTREATED ACUTE LYMPHOBLASTIC LEUKEMIA. A REPORT FROM CHILDRENS CANCER STUDY GROUP.

Nesbit ME, Sather H, Robison LL, Donaldson M, Littman P, Ortega JA, Hammond GD
Children's Cancer Study Group Operations Office, 1721 North Griffin Ave., Los Angeles, CA, 90031
Cancer Res; 42(2):674-680 1982

Between 1972 and 1974, Children's Cancer Study Group enrolled 724 children with newly diagnosed acute lymphoblastic leukemia on a single randomized clinical trial. Study CCG-101 was designed to test four types of presymptomatic central nervous system and sanctuary therapies consisting of (a) 2,400-rad craniospinal radiation therapy (RT) plus 1,200-rad extended-field RT, which included the liver, spleen, kidneys, lower abdomen, and gonads; (b) 2,400-rad craniospinal RT; (c) 2,400-rad cranial RT plus intrathecal methotrexate (it MTX); and (d) it MTX alone. Patients all received a 28-day induction course of vincristine, prednisone, and L-asparaginase and were maintained subsequently on a regimen consisting of daily 6-mercaptopurine, weekly MTX, and monthly pulses of vincristine and prednisone. Patients treated with six doses of it MTX alone had a significantly higher incidence of central nervous system relapse than did patien ts treated with 2,400-rad craniospinal RT plus 1,200-rad abdominal RT, 2,400-rad craniospinal RT, or 2,400-rad cranial RT plus it MTX. There was no significant difference in marrow remission duration or survival of the treatment groups. There appears to be a benefit with regard to length of bone marrow remission and survival for patients with initial white blood counts greater than 20,000/cu mm treated with cranial RT plus it MTX. The majority of the patients remaining on study have now discontinued maintenance therapy. The 8-yr overall estimated survival rate on this study is 56%, and the disease-free survival rate is 52%. (Author abstract) (27 Refs)

35. BUSULFAN, ANTIMETABOLITES, RADIOTHERAPY, AND COST OF TREATMENT IN CHRONIC MYELOCYTIC LEUKEMIA. A NON-CONTROLLED, NON-RANDOMIZED MONOCENTER STUDY WITH HISTORICAL CONTROLS.

Ogier C, Reizenstein P
Div. Hematology, Dept. Medicine, Karolinska Hosp., Stockholm, Sweden
Acta Med Scand; 210(5):409-413 1981

The possibilities were studied achieving remission more quickly, of preventing conceivably alkylator-induced blastic

transformation, and of prolonging survival in chronic myelocytic leukemia (CML) by replacing busulfan induction of remission by antimetabolite induction. The promise of the project was not considered to merit a prospective, controlled, randomized multicenter study, and therefore a retrospective, non-controlled, non-randomized pilot study was elected. One antimetabolite-treated group (cytosine arabinoside and thioguanine) and two busulfan-treated patient groups were studied. One of the latter two groups received splenic irradiation in addition to busulfan. No statistically significant differences between the busulfan groups were found in the time to achieve remission, the length of the first, unmaintained remission, the frequency of blastic metamorphosis or the cost of treatment. The actuarial survival curves of all three groups were similar. The antimetabolite induction was well tolerated and led to a statistically significantly more rapid remission than busulfan. However, the remission was significantly shorter, and no significant difference in the frequency of blastic metamorphosis was found between the groups. The median cost (from diagnosis to death) of hospitalization, visits, treatment, and part of the loss of production was approx 106,000 Sw cr in the busulfan + radiotherapy group, 116,000 in the busulfan group, and 178,000 in the antimetabolite group. It is suggested that a prospective, randomized, controlled study could confirm that the present antimetabolite induction may lead to a more rapid remission induction in CML without more side-effects. However, to prevent early relapse, antimetabolite induction should be combined with busulfan maintenance treatment. (Author abstract) (12 Refs)

36. THE COMPARISON OF TOTAL BODY IRRADIATION VS CHLORAMBUCIL AND PREDNISONE FOR REMI SSION INDUCTION OF ACTIVE CHRONIC LYMPHOCYTE LEUKEMIA: AN ECOG STUDY. PART I: TOTAL BODY IRRADIATION - RESPONSE AND TOXICITY.

Rubin P, Bennett JM, Begg C, Bozdech MJ, Silber R
Univ. Rochester Cancer Center, Rochester, NY
Int J Radiat Oncol Biol Phys; 7(12):1623-1632 1981

Total body irradiation (TBI) and chemotherapy (CPT) with chlorambucil (CA) and prednisone (PN) were compared for induction of remission in 52 patients with active chronic lymphocytic leukemia (CLL). Under Plan I 11 patients received 150 rads TBI/course (10 rads, 3 x/wk for 5 wk). Seven of 11 patients completed one course, three patients completed two courses, and one completed three courses. Under Plan II 15 patients received 50 rads/course (5 rads/day, 5 days/wk for 2 wk). Fourteen patients completed one course, 8 patients completed two courses, 2 patients completed three courses, and 1 patient completed five courses. Twenty-six patients received CPT (30 mg CA/square meter po 1 x/2 wk for 18 courses) or 9 mo, plus 80 mg PN for 5 days every 2 wk for 18 courses. No complete remissions (CR) were achieved by TBI; partial remissions were achieved in 73% of Plan I patients and 47% of Plan II patients. Life-threatening depression of granulocytes and/or platelets occurred in 73% of Plan I patients and 43% of Plan II patients. CPT achieved CR in 23% of cases and PR in 54%. CPT thus produced an overall response rate of 77% compared with 58% for TBI. Duration of response was 18 wk for TBI and 45 wk for CPT. Median survival times were not significantly different (136 wk for TBI and 135 wk for CPT). Results indicate that CPT is superior to TBI for improving the response rate, number of patients in remission, and median duration of response. (25 Refs)

SUPPORTIVE CARE

37. CRYOPRESERVATION AND SUBSEQUENT VIABILITY OF HUMAN BONE MARROW IN HEMATOLOGIC MALIGNANCIES: COMPARISON OF TWO DIFFERENT METHODS OF CELL RECONSTITUTION.

Porcellini A, Manna A, Manna M, Moretti L, Agostinelli F, Lucarelli G
Divisione di Ematologia, USL-3, Ospedale di Pesaro, Pesaro, Italy
Cryobiology; 18(6):541-546 1981

Bone marrow cells collected from patients with hematologic malignancies were cryopreserved using DMSO as a cryoprotective agent. The growth kinetics of hemopoietic stem cells frozen to-196 C was monitored immediately after thawing by the semisolid agar CFU-C assay and two different methods of cell reconstitution were compared. In the first procedure, thawed cells were plated after the removal of DMSO by washing the cell suspension; in the second, cell suspensions were cultured after a simple 1:1 dilution of DMSO with medium. The numbers of CFU-C per 2 x 10(5) cells plated was higher by washing out the DMSO in all the groups studied. However, the absolute numbers of CFU-C contained in the whole ampules after the freezing procedures was approx the same using both methods. It is concluded that washing the cells only apparently yielded a better cloning efficiency, suggesting that such a procedure led to a higher mature nucleated cell loss with the consequence of a CFU-C concentration. This trend seems particularly evident in cells from the AML and CML patients. (Author abstract) (19 Refs)

38. SERIOUS INFECTIONS DURING CONTINUING TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA.

Ninane J, Chessells JM
Dept. Hematology, Hosp. for Sick Children, Gt Ormond St., London WC1N 3JH, England
Arch Dis Child; 56(11):841-844 1981

Seventy-six of 168 children with acute lymphoblastic leukemia, who had completed induction therapy and central nervous system prophylaxis, were each admitted to hospital at least once during subsequent treatment with an infectious illness. The time spent in hospital was calculated as a proportion of the total number of days at risk and had a mean value of one day in 75. Sixty-three (37%) children spent longer than this in hospital, particularly patients younger than 5 years and those on a more intensive protocol; a 3rd year of treatment appeared to carry no significant additional risk of infection. Death due to infection occurred in 14 (8.3%) children; these deaths were more common in younger patients and during the first 2 years of treatment and were mainly due to measles, septicemia, or cytomegalovirus. These findings show that younger children and those receiving more intensive treatment are at greater risk of infection. The risk is not one of exotic infections, but of measles, a preventable disease. (Author abstract) (15 Refs)

39. THE ORAL FLORA AS A SOURCE OF SEPTICEMIA IN PATIENTS WITH ACUTE LEUKEMIA.

Greenberg MS, Cohen SG, McKitrick JC, Cassileth PA
Dept. Dental Medicine, Hosp. Univ. Pennsylvania, Box 654, 3400 Spruce St., Philadelphia, PA, 19104
Oral Surg; 53(1):32-36 1982

This study was performed to determine the role of the oral cavity in causing septicemia in patients with acute leukemia. Thirty-three patients with acute nonlymphocytic leukemia were investigated prospectively via clinical, hematologic, and microbiologic techniques. The mouth was the most likely source of septicemia in 7 of 12 cases. Necessary dental treatment prior to chemotherapy was accompanied by a significant reduction in the rate of septicemia. The authors concluded that oral sources of bacteremia should be eliminated prior to chemotherapy in patients with acute leukemia. (Author abstract) (23 Refs)

40. CO-TRIMOXAZOLE ALONE FOR PREVENTION OF BACTERIAL INFECTION IN PATIENTS WITH ACUTE LEUKEMIA.

Starke ID, Catovsky D, Johnson SA, Donnelly P, Darrell J, Goldman JM, Galton DA
Medical Res. Council Leukemia Unit, Royal Postgraduate Medical Sch., London W12 OHS, England
Lancet; 1(8262):5-6 1982

Forty-three patients undergoing treatment for acute leukemia were randomized to receive either co-trimoxazole alone or co-trimoxazole with framycetin and colistin as antibacterial prophylaxis during periods of neutropenia. There were no significant differences between the two treatment groups in the time before the onset of the first fever, the number of episodes of fever or of septicemia per patient, the number of neutropenic days during which patients remained afebrile or did not require systemic antibiotics, or the number of resistant organisms acquired. Co-trimoxazole alone is cheaper and easier to take than co-trimoxazole with framycetin and colistin, and it is therefore preferable to the three-drug combination for the prophylaxis of bacterial infection. (Author abstract) (9 Refs)

41. CO-TRIMOXAZOLE VERSUS NON-ABSORBABLE ANTIBIOTICS IN ACUTE LEUKEMIA.

Watson JG, Powles RL, Lawson DN, Morgenstern GR, Jameson B, McElwain TJ, Judson I, Lumley H, Kay HE
Dept. Paediatrics, Royal Free Hosp., Pond St., London NW3 2QG, England
Lancet; 1(8262):6-9 1982

In a single-center prospective trial patients with acute myeloid leukemia in protective isolation and undergoing remission induction or allogeneic bone-marrow transplantation were randomized to receive one of two prophylactic antibacterial regimens-absorbable co-trimoxazole or non-absorbable neomycin plus colistin. Co-trimoxazole prevented infection more effectively and was associated with less gastrointestinal disturbance, but it may have caused some bone-marrow suppression. (Author abstract) (20 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

42. HAIRY CELL LEUKEMIA IN THREE SIBLINGS: AN APPARENT HLA-LINKED DISEASE.

Wylin RF, Greene MH, Palutke M, Khilanani P, Taboczka P, Swiderski G
Harper Hosp., 3990 John R. St., Detroit, MI, 48201
Cancer; 49(3):538-542 1982

In a sibship of 11 adults the HLA haplotype A1, B7 occurred in four brothers, three of whom developed hairy cell leukemia (HCL) within a 7-year period. While this haplotype does not appear to occur with increased frequency in random cases of HCL, the fact that three cases of this uncommon and unique disorder occurred within one family and affected siblings with a common haplotype strongly suggests a genetic linkage. (Author abstract) (21 Refs)

SELECTED PRE-CLINICAL STUDIES

43. MONOCLONAL ANTIBODY SPECIFIC FOR HUMAN T ACUTE LYMPHOBLASTIC LEUKEMIA.

Deng CT, Chia J, Terasaki P, Billing R
Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Lancet; 1(8262):10-11 1982

A cytotoxic mouse monoclonal antibody (CALL2) was produced against a cultured T acute lymphocytic leukemia (T ALL) cell line 8402. Ascites fluid containing the antibody was cytotoxic to a titer of up to 1:100,000 against four of six cultured T ALL cell lines and against leukemia cells from seven of eight T ALL patients and one of five T chronic lymphatic leukemia patients. The antibody did not react with normal peripheral-blood T and B lymphocytes, monocytes, granulocytes, spleen cells, thymocytes, platelets, and other acute and chronic leukemia cells. The CALL2 antibody did not react with bone marrow stem cells of the myeloid series (CFU-C). This antibody may be useful for passive immunotherapy trials since it does not react with normal cells and is highly cytotoxic to T ALL cells. (Author abstract) (9 Refs)

44. MONOCLONAL ANTIBODY-RICIN A CHAIN CONJUGATE SELECTIVELY CYTOTOXIC FOR CELLS BEARING THE COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN.

Raso V, Ritz J, Basala M, Schlossman SF
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
Cancer Res; 42(2):457-464 1982

The toxic subunit of ricin has been conjugated by a disulfide bone to a monoclonal murine antibody (J-5) specific for the common acute lymphoblastic leukemia antigen (CALLA) expressed on human lymphoblastic leukemia cells. Both the monoclonal antibody and ricin A chain retained their original biological activity after conjugation. The ricin A chain antibody-combining site attached to the membrane of CALLA-bearing cells, whereupon both components of the molecule, antibody and A chain, could be detected using fluorescein-labeled antibody probes directed against either mouse F(ab')2 or ricin A chain. This conjugate proved to be a potent cytotoxin for CALLA-positive Nalm-1 cells growing in vitro and produced

50% inhibition of proliferation at levels of 2 x 10(-10) M. CALLA-negative cell lines were unaffected until levels of conjugate approached 10-6 M. When tested for cytotoxic action on Nalm-1 cells, the composite conjugate molecule was at least 2,000x more effective than J-5 antibody alone, ricin A chain alone, or a noncovalent mixture of these components. Cytotoxicity of the conjugate could be blocked completely by addition of antibodies specific for either mouse Ig or ricin A chain. Direct comparison of the in vitro cytotoxity of CALLA-directed univalent Fab versus bivalent F(ab')2 carriers of ricin A chain revealed 70-fold greater efficacy for the latter conjugate. This differential could not be accounted for by differences in A chain activity or binding affinity for the cell membrane but appeared related to the ability of the multivalent agent to induce modulation and internalization of CALLA determinants. No overt toxic effects were noted when the F(ab')2-A chain conjugates was administered iv to rabbits at levels as high as 20 mg/kg single injection or 5 mg/kg for 5 days. The unique specificity characteristics and high potency of this cytotoxic conjugate indicate that it has significant therapeutic potential for the treatment of CAI LA-bearing human leuke mias and lymphomas. (37 Refs)

45. ALLOIMMUNIZATION AND ADOPTIVE IMMUNOTHERAPY OF LEUKEMIA.

Truitt RL, Shih CY, Rimm AA, Tempelis LD, Bortin MM, Dutton RW, Altmann A, Alexander P, Martin WJ, Rajan
Winter Res. Lab., Mount Sinai Medical Center, P.O. Box 342, Milwaukee, WI, 53201
Transplant Proc; 13(4):1910-1914 1981

Factors that affect induction of graft-vs-leukemia (GVL) reactivity (against AKR-L) in alloimmunized CBA/J mouse donors are described. Spleen cells from unimmunized or isoimmunized CBA donors had no GVL reactivity; 178/179 AKR secondary recipients died of leukemia within 90 days. CBA donors that were alloimmunized with viable lymphoid cells from H-2-compatible or -incompatible mice exhibited high levels of GVL reactivity. Immunization with lymphoid cells from H-2-compatible mice induced significantly higher levels of GVL reactivity than did lymphoid cells from H-2-incompatible mice. Irradiation of AKR-L or lymphoid cells from H-2-compatible donors significantly reduced the GVL reactivity induced in CBA donors in comparison with unirradiated cells. Heat treatment of alloimmunizing cells also significantly impaired induction of GVL reactivity. Inactivation of lymphoid cells with mitomycin C caused nc significant reduction in their ability to induce GVL reactivity. Significant GVL reactivity was observed after alloimmunization with purified C3H/He (H-2k) epidermal cells but not with BALB/c (H-2d) cells. Antigens and mechanisms involved in GVL reactivity are discussed. (21 Refs)

46. T-CELL GROWTH FACTOR (INTERLEUKIN 2) CONTROL OF T-LYMPHOCYTE PROLIFERATION: POSSIBLE INVOLVEMENT IN LEUKEMOGENESIS.

Gillis S, Mertelsmann R, Moore MA
Basic Immunology Program, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Transplant Proc; 13(4):1884-1890 1981

Isolation of murine and human leukemic T-cell lines that produce exceptionally high quantities of interleukin 2 (IL-2), and screening of freshly isolated patient-derived human leukemic blasts for IL-2 production and response capabilities, are described. An IL-2 microassay was used to screen fractions of biochemically manipulated, conditioned medium for the capacity to promote sustained in vitro proliferation of murine cytotoxic T-lymphocytes. Two leukemic cell lines, murine LBRM-33 and human Jurkat-FHCRC, produced large quantities of IL-2 upon stimulation with phytohemagglutinin (PHA). Both of the cell lines bear conventional T-cell markers and phenotypic markers indicative of immature cell type. Analysis of leukemic blast cell response of mononuclear blood cells from patients with various leukemias revealed consistent IL-2 production and response patterns. All patients who exhibited high levels of deoxynucleotidyl transferase (TdT) in leukemic blood cells showed a small proliferation increase in response to PHA stimulation but produced exceptionally high levels of IL-2. The response to added purified human IL-2 and PHA was atypical in most patients, in that incorporation of 3H-thymidine decreased in the majority of TdT+ leukemias when compared to PHA-stimulated proliferation. Such a finding was in marked contrast to results obtained with normal lymphocytes. IL-2 production and use responses and TdT expression in leukemic cells are discussed. (17 Refs)

47. FURTHER EVIDENCE FOR LOSS OF GROWTH POTENTIAL DURING MOUSE MYELOID LEUKEMIA (M1) CELL DIFFERENTIATION.

Sakagami H, Unten S, Konno K
Dept. Biochemistry, Sch. Medicine, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Cell Struct Funct; 6(3):289-293 1981

The relationship between cell differentiation (CD) and growth potential was studied in vitro in mouse myeloid leukemia M1 cells of clone T22. CD was induced by treating cells with dexamethasone (DMS: 0-3 x 10(-5) M). Phagocytic activity (PA) was measured by incubating 10(6) cells with polystyrene latex particles (av diameter 0.81 microns, in 3.3 ml serum-free medium) and counting the particles phagocytized by the cells. Lysozyme activity (LA) was measured by the micrococcus lysoplate technique. DNA synthesis (DNAS) was measured by [6-3H]thymidine labeling. PA was detectable 22 hr after DMS treatment and reached a peak at 65 hr. Minimum DNAS and max PA were produced at a concentration of 3 x 10(-7)-10(-6) M DMS; adding further DMS did not totally eliminate DNAS and left 40% of cells undifferentiated. Plotting PA against DNAS produced similar curves whether PA was plotted as the % of cells showing PA or as the number of particles phagocytized/cell. PA increased if DNAS decreased. In comparing LA and DNAS, minimum DNAS and max LA were produced at a concentration of 10(-6) M DMS; adding further DMS did not further affect DNAS or LA. A negative correlation between LA and DNAS was noted, with LA appearing 2-3 days after treatment. Results, combined with previous findings, indicate the probability that properties associated with differentiated cells (PA and LA) are exhibited exclusively by non-replicating cells. (10 Refs)

REVIEWS

48. PRELEUKEMIA.

Levitt RC, Stuart RK
Dept. Medicine, Johns Hopkins Hosp., Baltimore, MD
Johns Hopkins Med J; 148(5):200-204 1981

Clinical features, pathogenesis, and treatment of the preleukemia syndrome (PLS) are reviewed and a case history pre-

sented. PLS possesses distinct clinical and diagnostic criteria. Some prerequisites include anemia and oval macrocytosis in peripheral blood (PB), megaloblastoid erythropoiesis and/or disorderly granulopoiesis, and absence of overt findings of leukemia in bone marrow (BM). Among corroborative findings are nucleated RBC, hypochromia, bizarre platelet size, and reduced platelets and neutrophils in PB; BM will show erythrocytic and megakaryocytic hyperplasia. Review of two recent prospective series indicates significant risk (20-25%) of development of acute nonlymphocytic leukemia in patients with PLS, with av time to acute leukemia of less than 2 yr. High excess mortality exists with these patients, especially due to infection or bleeding. A 52-yr-old male patient presented with a hematocrit of 24%, platelets of 14,000/cubic mm, and 2,400 WBC/cubic mm, with 3% blasts, 1% juveniles, no neutrophils, 87% lymphocytes, 5% monocytes, and 4% eosinophils. Thirteen nucleated RBC/100 WBC were counted, and hypochromasia was noted in the peripheral smear; striking anisocytosis and poikilocytosis with frequent oval macrocytes and microcytes were seen. BM showed hypercellularity, evidence of erythroid hyperplasia, rare megakaryocytes, abnormal erythropoiesis, arrest of myeloid maturation, and defective neutrophil granulation. The Diagnosis of PLS was confirmed and the patient was referred for treatment of acute leukemia. (25 Refs)

49. THE CHRONIC LEUKEMIAS.

Rosenthal DS, Moloney WC
Harvard Medical Sch., Boston, MA
Curr Ther; 28:318-320 1981

Care of patients with chronic granulocytic leukemia (CGL) is described. Therapy occurs in three phases: early (or preclinical), active, and blast crisis. CGL in the early phase is asymptomatic. Treatment modalities used in the active phase and staging by the Rai modification are detailed. Blast crisis occurs in greater than 80% of cases and is generally resistant to aggressive therapy. While median survival during the active phase is 40 mo, that in the blastic crisis is measured in weeks. Terminal deoxynucleotidyl transferase-positive blast crisis patients are treated like those with acute lymphoblastic leukemia. The need for treatment of chronic lymphocytic leukemia (CLL) is indicated not only by elevated WBC count, but by appearance of anemia, thrombocytopenia, enlarged lymph nodes, splenomegaly, or invasion of the marrow or viscera. Rai staging of CLL clarifies timing of treatment and prognosis. In Stages III and IV, anemia and thrombocytopenia are related to marrow infiltration and are not secondary to an immune mechanism; as in the preclinical phase of CGL, Stages 0, I, and II disease need not be treated. Large nodes or splenomegaly causing compressive symptoms may be treated with chemotherapy or local irradiation. In the more aggressive Stages III and IV, intensive therapy like that used in non-Hodgkin's lymphoma may be necessary. Immune complications of CLL are treated by prednisone and splenectomy if no response has been obtained with corticosteroids. (no Refs)

50. CHILDHOOD ACUTE LEUKEMIA.

Miller DR
Memorial-Sloan Kettering Cancer Center, New York, NY
Curr Ther; 28:309-318 1981

Diagnosis, prognosis, supportive care, anemia, hemorrhage, infection, electrolyt e imbalance, and hyperuricemia in various acute leukemias of childhood are discussed. Specific therapy of acute lymphoblastic leukemia (ALL; induction, extramedullary leukemia) and acute nonlymphoblastic leukemia (ANLL; induction, psychosocial support) is detailed. Design of treatment strategy in childhood acute leukemia requires accurate diagnosis using morphologic criteria, histochemical stains, and characterization of the immunologic cell surface. Prognosis in childhood ALL is determined by clinical and biologic features identified at or early after diagnosis. While morphologic subtypes in ANLL are not prognostic, a better rate of complete remission induction is found in patients 5-10 yr old with initial WBC less than 20,000/ul. In most leukemias certain general measures are required to restore physiologic homeostasis at time of diagnosis. Chemotherapy for acute leukemia in childhood and side effects and drug toxicity are detailed. (no Refs)

51. ACUTE LEUKEMIA IN ADULTS.

Preisler HD
Roswell Park Memorial Inst., Buffalo, NY
Curr Ther; 28:306-309 1981

Evaluation and treatment of patients with acute leukemia are discussed. The patient should be carefully and completely evaluated since the results of the initial work-up dictate the therapeutic approach. Any febrile leukemic patient should be assumed to be infected unless proved otherwise. Regardless of the physical findings, febrile patients with 500 or fewer circulating granulocytes should be treated immediately with broad-spectrum antibiotics. Patients who remain persistently febrile despite antibiotic therapy should receive granulocyte transfusions containing at least 10(10) granulocytes/transfusion. Treatment of disseminated intravascular coagulation and elevated blast cell counts are described. Remission induction should be administered to most patients with acute lymphocytic leukemia; possible exceptions are patients greater than 70 yr old and patients with oligoblastic leukemia. Induction chemotherapy regimens for acute lymphocytic (allopurinol, daunorubicin, vincristine, prednisone, and L-asparaginase) and acute myelocytic (daunorubicin and cytosine arabinoside) leukemias are reported. Maintenance chemotherapy regimens also are described. Infection is the major complication of remission induction therapy. Drug dosages should be modified in patients with liver and renal diseases and in those with congestive heart failure. Use of prophylactic CNS therapy is discussed. Therapeutic approaches under development for the treatment of acute leukemias are discussed. (no Refs)

52. CLINCO-MORPHOLOGICAL CLASSIFICATION OF ACUTE LEUKEMIAS.

Maldonado J, Ramirez G, Artacho MC
Servicio de Hematologia y Hemoterapia, C.S. 'Carlos Haya' de la S.S., Malaga, Spain
Sangre (Barc); 26(5C):946-962 1981

The important advances attained in the last 10 yr on the acute leukemia cell hav e introduced striking modifications in the classification of, and subsequently the therapeutical strategy for, this disease. This cytomorphological classification proposed by WHO in 1973 has been displaced by that devised in 1976 by the FAB cooperative group. Modifications to the FAB proposal concerning both myeloid and lymphocytic leukemias have emerged in 1980 and 1981 with the assistance of cytochemical techniques. The new criteria have been applied by the authors to fifty cases of each acute leukemia variety in order to establish base-line comparisons. Histological bone-marrow studies, electron microscopy, and automation of blood differential count are diagnostic tools to be applied in the classification of leukemic cells. Cytogenetics, cell-culture techniques, and cell kinetics are further paths to follow in acute leukemia identification. However, the most striking progress in this field

comes from the discovery of cell membrane- and enzyme-markers, giving rise to a new immunologic classification of acute lymphoblastic leukemia. The clinical profile of acute leukemia represents a landmark in the classifications when prognostic purposes are sought, so finding the possible correlations between all study methods is one of the aims of the present report: in this connection, the existing protocols have been applied by the authors to one-hundred patients of each leukemia variety. The special forms of acute leukemia are finally considered on the bases of the diagnostic advances commented above, in an attempt to re-evaluate such forms. This review was made as an introduction to the round-table conference in which other contributors will undoubtedly focus their attention on the topics concerning acute leukemia. (Author abstract) (40 Refs) (In SPA)

53. MARKERS OF CELLULAR DIFFERENTIATION IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Pelper SC, Stass SA
Div. Pathology, St. Jude Children's Res. Hosp., 332 N Lauderdale, PO Box 318, Memphis, TN, 38101
Arch Pathol Lab Med; 106(1):3-8 1982

Acute lymphoblastic leukemia (ALL) is a heterogeneous entity that can be subcategorized on the basis of morphologic aspects, immunologic markers, membrane antigens, and enzymatic content of the blast forms. Subgroups corresponding to T-cell, pre-T-cell, pre-B-cell, and non-T-, non-B-lymphocyte derivations can be defined by immunologic markers, and the biologic differences are supported by the differential expression of membrane antigens and of nuclear, lysosomal, cytoplasmic, and membrane enzymes. These studies ease the diagnosis and characterization of ALL and enhance understanding of this disease. (Author abstract) (81 Refs)

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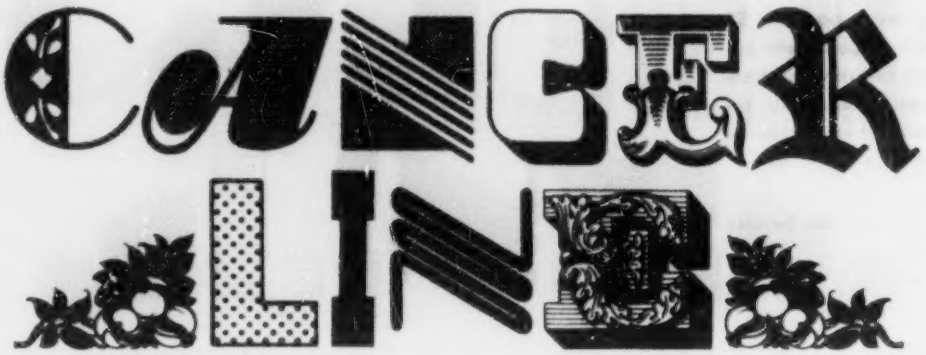

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DIAGNOSIS

1. DIAGNOSTIC CONCURRENCE IN THE SUBCLASSIFICATION OF ADULT ACUTE LEUKEMIA USING FRENCH-AMERICAN-BRITISH CRITERIA.

Dick FR, Armitage JO, Burns CP
Dept. Pathology, Univ. Iowa, 166 Medical Lab., Iowa City, IA, 52242
Cancer; 49(5):916-920 1982

Using FAB criteria, we retrospectively classified 195 adult acute leukemia cases seen over a 6-yr period. Acute lymphoblastic leukemia (ALL) was separated from acute nonlymphoblastic leukemia (ANLL) by negative peroxidase. The dysmyelopoietic syndrome was separated from ANLL when the per-

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centage of immature leukemic cells was less than 30%. The 55 cases of ALL and 140 cases of ANLL thus defined were initially independently subclassified with Wright's stained smears by three observers. Cases were then jointly reviewed by using all available information, and a final consensus diagnosis was reached. For ALL, there was complete agreement (of initial independent observations) about subtype in 32 of 55 (58%); for only one case was there total disagreement. For ANLL there was complete agreement in 89 of 140 (64%) and total disagreement in 5 of 140 (4%). Frequent disagreement of independent observations with the consensus diagnosis were L1 interpreted as L2, M5 interpreted as M4, L3 interpreted as L2, L2 interpreted as L1, M1 interpreted as M2 and M4 interpreted as M5. Although there appears to be variation between observers, all but 6 of 195 cases had at least two observers in agreement. Disagreement appeared to be partly based on varying interpretations of subjective criteria and partly on the variability in determining percentages of cell types present. The use of nonspecific esterase stain or lysozyme appeared to improve diagnostic agreement over that observed using Wright's stained slides alone in approx 5% of cases of ANLL. (Author abstract) (12 Refs)

2. CHRONIC LYMPHOCYTIC LEUKAEMIA: A TEST OF A PROPOSED NEW CLINICAL STAGING SYSTEM.

Geisler C, Hansen MM
Medical Dept., Finsen Inst., 49 Strandboulevarden, DK-2100 Copenhagen 0, Denmark
Scand J Haematol; 27(4):279-286 1981

One hundred two patients with chronic lymphocytic leukemia underwent clinical staging according to two systems: the Rai staging system with five stages (0: lymphocytosis, I: palpable lymph nodes, II: hepato- or splenomegaly, III: Hb below 110 g/l, IV: platelet count below 100 x 10(9)/l) was compared to a staging system recently proposed by Binet, with only three stages (A: not more than 2 areas of palpable nodes or organs, B: at least 3 areas, C: Hb below 10 g/l or platelet count below 100 x 19(9)/l). With the three-stage system statistically significant differences between the stages were obtained, whereas some of the Rai stages (I-II-III) were only poorly separated. Non-hemolytic anemia with Hb below 100 g/l was associated with a far graver prognosis than milder anemia (Hb between 100 and 110 g/l) or auto-immune hemolytic anemia. Chest x-ray findings did not influence the clinical stage. (Author abstract) (12 Refs)

3. ACUTE PROMYELOCYTIC LEUKAEMIA: A STUDY OF 39 CASES WITH IDENTIFICATION OF A HYPERBASOFHILIC MICROGRANULAR VARIANT.

McKenna RW, Parkin J, Bloomfield CD, Sundberg RD, Brunning RD
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 198, Mayo Memorial Building, Minneapolis, MN, 55455
Br J Haematol; 50(2):201-214 1982

Thirty-nine cases of acute promyelocytic leukemia (APL) were divided into two morphological subgroups, typical hypergranular APL (31 cases) and microgranular APL (8 cases, 21%). The leukemic cells in the microgranular APL cases were characterized by striking nuclear folding or lobulation; granulation was present in most of these cells but was less abundant and finer than in typical APL. In three microgranular APL cases a distinctive small leukemic promyelocyte with unusual nuclear lobulation and deeply basophilic cytoplasm containing few or no visible granules was the predominant leukemic cell. This small hyperbasophilic promyelocyte was also present as a minor population of cells in the other five microgranular APL cases and in 28 of the 31 typical APL cases. Ultrastructurally the most abundant promyelocytes in microgranular APL had smaller and usually fewer granules than in typical APL; other characteristic ultrastructural features of APL were found with equal frequency. The median blood leukocyte count was significantly higher in microgranular APL, 83.0 x 10(9)/l, than in typical APL, 1.8 x 10(9)/l (p less than 0.01). The median duration of complete remission (CR) for microgranular APL, 6.5 mo, was shorter than the 21+ mo median CR for typical APL. The morphological characteristics of microgranular APL may mimic those of myelomonocytic leukemia; however, the presence of cells with multiple Auer rods, large inclusions of Auer-like material and the small hyperbasophilic promyelocytes are important distinguishing features. In equivocal cases cytochemistry, electron microscopy and cytogenetic studies may verify the diagnosis. (Author abstract) (32 Refs)

4. PROGNOSTIC SIGNIFICANCE OF THE PAS REACTION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Wachowiak J
I Klinika Chorob Dzieci, Institut Pediatrii AM, ul. Szpitalna 27/33, 60-572 Poznan, Poland
Pediatr Pol; 56(9):1009-1015 1981

The prognostic significance of the PAS reaction of bone marrow cells was studied in 71 untreated children (8 mo to 16 yr old) with acute lymphoblastic leukemia (ALL) during the initial phase of the disease before intensive polychemotherapy and preventive cranial irradiation. The PAS scores av 52.7 (0-245 scores). The av PAS scores were 29.3 for the 28 patients with remissions lasting 2 yr or less and 94.0 for the 26 patients with remissions lasting more than 2 yr. The av PAS scores were 31.8 for the 22 childen who survived less than 2 yr and 92.0 for the 16 children who survived more than 3 yr. The differences in the PAS scores were statistically significant between the patients with short and long remission and between those surviving more than 3 yr and less than 3 yr. The av PAS scores were 73.1 in the 36 patients with initial leukocyte counts of 10,000/cubic mm (mm3) or less, 38.6 for the 19 patients with 10,000-49,999/mm3 and 22.6 for the 16 patients with 50,000/mm3 or more. The findings indicate that strongly positive PAS reaction of bone marrow cells is a favorable prognostic sign in children with ALL. (21 Refs) (In POL)

5. ALTERATION IN THE REGULATORY AND REDOX BEHAVIOR OF HUMAN ACUTE LEUKEMIC MYELOID CELLS FOLLOWING RELAPSE.

Ghosh AK, Evans AE, Ghosh S, Clark M
Dept. Biochemistry and Biophysics, G3 Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Cancer Biochem Biophys; 5(4):253-258 1981

Acute myeloid leukemia (AML) cells obtained from peripheral blood of patients, and containing more than 90% blast cells, were used in studies of cellular metabolic control before and after relapse. The rate of lactate production and the lactate:pyruvate ratio were higher in cells at diagnosis than after relapse, and Pasteur and Crabtree control values were higher in cells after relapse than before. In a single patient, the Pasteur and Crabtree control values of AML cells during relapse were much higher than those obtained before chemotherapy. Rates of lactate production, oxygen uptake, and lactate:pyruvate ratio in the aerobic state decreased in these cells during relapse. Rate of oxygen utilization in the uncou-

pled state (respiratory potential) increased dramatically during relapse. ATP/ADP ratios increased in later periods of relapse. Redox behavior of AML cells measured by NADPH fluorescence clearly showed alterations in the glycolytic behavior (regulation) of the cells during relapse after treatment. The Pasteur control of AML cells in relapse indicated strong regulation of aerobic glycolysis at the phosphofructokinase step, but NADPH fluorescence pattern indicated gradual changes in glycolysis regulation beyond glyceraldehyde 3-phosphate dehydrogenase, presumably at the phosphate kinase step. (14 Refs)

6. SIALYLTRANSFERASE ACTIVITY AS A MARKER FOR THE DIFFERENTIATION OF LYMPHOCYTES. INCREASE IN SIALYLTRANSFERASE ACTIVITY OF BLASTS FROM ACUTE LYMPHOBLASTIC LEUKAEMIA CASES BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA).

Sasaki R, Takaku F, Lin YL, Bollum FJ
Dept. Hematology, Jichi Medical Sch., 3311-1 Yakushiji Minamikawachi-Machi, Kawachi-Gun, Tochigi 329-04, Japan
Clin Exp Immunol; 47(2):381-388 1982

The level of sialyltransferase activity in leukemic blasts from acute lymphoblastic leukemia (ALL) cases was significantly lower (3.29 +-2.09 pmoles/5 x 10(7) cells or 1.77 +-1.16 pmoles/mg protein) than those (18.80 +-4.91 pmoles/5 x 10(7) cells or 7.72 +-1.75 pmoles/mg protein) of mature lymphocytes from normal volunteers (t less than 0.001). An inverse relationship between the level of sialyltransferase activity and the level of terminal transferase (TdT) activity was seen in blasts from eight TdT-positive ALL cases. No significant difference was observed in the level of sialyltransferase activity between ALL and cells of chronic myelogenous leukemia (CML) in blast crisis. Short term culture of ALL blast cells with 12-O-tetradecanoylphorbol-13-acetate (TPA) at the concentration of 10(-6) M to 1 0(-9) M caused a marked increase in sialyltransferase activity. In one of these three ALL cases the population of TdT-positive cells and the TdT activity of the blasts decreased significantly after culture with TPA. These results suggest that biochemical differentiation of leukemic lymphoblasts has been induced by the addition of TPA, although morphological changes were not observed. Sialyltransferase activity may be a useful indicator for the analysis of differentiation of lymphocytes. (Author abstract) (25 Refs)

7. DETERMINATION OF ULTRASTRUCTURAL PEROXIDASES AND IMMUNOLOGIC MEMBRANE MARKERS IN THE DIAGNOSIS OF ACUTE LEUKEMIAS.

Marie JP, Perrot JY, Boucheix C, Zittoun J, Matyre MC, Kayibanda M, Rosenfeld C, Mishal Z, Zittoun R
Service d'Hematologie, Hotel Dieu, 1 place du Parvis Notre Dame, 75181 Paris Cedex 04, France
Blood; 59(2):270-276 1982

Detection of membrane markers and ultrastructural peroxidase activity was carried out on the blasts of 16 apparently nonmyeloid adult acute leukemias. These patients were selected from 73 adult leukemic patients by the negativity of their routine cytochemical myeloid markers: ie, myeloperoxidase, cholesterase activity, and Sudan Black B staining. B and T acute lymphoid leukemias (ALL) were excluded from the study. After concurrent testing from human T lymphocyte antigen (HuTLA), common ALL antigen (cALL), Ia-like antigens, and peroxidase activity at the electron microscopic level (POEM), only two patients remained undifferentiated (cALL-, POEM-). Two other cases were classified as following: six common ALL (cALL+, POEM-), one pre-T-ALL (cALL+, HuTLA+, POEM-), five very poorly differentiated acute myelogenous leukemia (AML) (cALL-, POEM+), and two mixed leukemias (cALL+, POEM+). Terminal deoxynucleotidyl transferase activity (TdT) was measured in seven cases and was found to be present at high levels in four cases of cALL and in the two cases of acute undifferentiated leukemias (AUL); it was absent in two cases of AML. Cytogenetic analysis had showed that 2 of the cALLs, three of the AMLs, and the two mixed leukemias were Ph1+. We conclude that POEM detection is useful in apparently nonmyeloid leukemias with negative immunologic lymphoid markers, and that the existence of a Ph+ chromosome should be investigated, particularly in the unusual case of mixed (lymphoid-myeloid) acute leukemia. (Author abstract) (24 Refs)

8. PRODUCTION OF IMMUNOREACTIVE CALCITONIN BY MYELOID LEUKAEMIA CELLS.

Foa R, Oscier DG, Hillyard CJ, Incarbone E, McIntyre I, Goldman JM
(c/o Oscier) MRC Leukemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 0HS, England
Br J Haematol; 50(2):215-223 1982

Raised plasma levels of immunoreactive human calcitonin (i-HCT) have been found in patients with chronic granulocytic leukemia (CGL) in chronic phase and myeloblastic transformation and in patients with acute myeloid leukemia at presentation and in relapse. In CGL levels were significantly higher in myeloblastic transformation than in the chronic phase. Leukemia cells were cultured in a short-term liquid culture system in which little cell proliferation occurs and in a two layer blast-cell colony system which permits blast-cell proliferation. i-HCT was identified in supernatant media from cells cultured in both systems but levels were substantially higher in media collected from cells cultured in the latter system. These results suggest that i-HCT is synthesized by proliferating blast cells. (Author abstract) (7 Refs)

9. FLOW CYTOMETRIC ANALYSIS OF CELLULAR DNA IN HUMAN ACUTE NONLYMPHATIC LEUKEMIAS AND DYSMYELOPOIETIC SYNDROMES.

Maiolo AT, Fao P, Mozzana R, Chiorboli O, Ciani A, Maisto A, Starace G
Clinica Medica I, Univ. Milan, Milan, Italy
Cytometry; 2(4):265-267 1982

Cell cycle distribution in bone marrow specimens from untreated overt myeloid leukemias (ANLL; 16 patients) and dysmyelopoietic states (8 refractory anemias with excess blasts and 5 idiopathic refractory sideroblastic anemias) was studied. The DNA-flow cytometric patterns of leukemic cells in bone marrow aspirates and in vitro after culture on dialysis membranes were compared. No significant difference was found between the cell cycle distribution in ANLL and dysmyelopoietic states. Centrifugation can improve the percentage of immature proliferating cells in bone marrow; elutriation may be more effective. In ANLL, no relationship between the percentage of blast cells in the marrow and the size of the S phase compartment could be observed. Size of the S phase compartment was related to the in vitro growth of leukemic cells in liquid culture. When leukemic cells were cultured in vitro on dialysis membrane, the proliferation profile of the original sample was kept relatively constant. This in vitro technique allows myeloid cells to grow actively without any supply of exogenous stimulators, easy cell recovery for assessment of cell

morphology and cytochemistry, and flow cytometry measurements. (12 Refs)

10. DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF CHROMOSOME ABNORMALITIES IN MARROW AND MITOGEN RESPONSE OF LYMPHOCYTES OF ACUTE NONLYMPHOCYTIC LEUKEMIA.

Shiraishi Y, Taguchi H, Niiya K, Shiomi F, Kikukawa K, Kubonishi S, Ohmura T, Hamawaki M, Ueda N
Lab. Clinical Cytogenetics, Dept. Anatomy, Kochi Medical Sch., Nankoku-City, 7-1-51, Kochi, Japan
Cancer Genet Cytogenet; 5(1):1-24 1982

Chromsomes of bone marrow from 28 patients with acute nonlymphocytic leukemia (ANLL) (26 with AML, 2 with AMMoL), 19 of whom had chromosome abnormalities, were studied; 11 cases exhibited previously unreported karyotypic abnormalities. The marrows of two cases had 8-21 translocations associated with an iso-X chromosome in the female patient and with 9q13-and a missing Y in the male patient. Usually, AML patients with an 8-21 translocation have been considered to have a good prognosis; however, our cases had rather short survival times. Therefore, the prognosis of AML with an 8-21 translocation but associated with other abnormalities is still not clear. Centromere spreading (CS), which was originally reported in marrow cells of megaloblastic anemia (B12 and folic acid deficiency), was detected in leukemic cells, disappeared during remission, and reappeared on relapse. These findings suggest that CS may be a new type of abnormality in AML. In two patients with atypical hypoplastic anemia and hemolytic anemia, chromosome abnormalities were detected at the anemic stage. One case with CS was associated with atypical hypoplastic anemia and developed AML after 1 yr; the other with 48,XY,+i(1q),+3,+12 and-14 had hemolytic anemia and developed AMMoL 3 wk later. Interestingly, identical clones were detected both before and after the clinical diagnosis of leukemia. These cases strongly support the concept that some chromosome abnormalities precede the clinical manifestations of leukemia. The present study also revealed that lymphocytes in ANLL respond poorly to PHA in the presence of high numbers of blasts but do respond well to mitogens during remission. Therefore, the response of lymphocytes to PHA may serve as one criterion for determining remission. (Author abstract) (15 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

11. IMMUNOLOGIC CLASSIFICATION OF LYMPHOCYTIC LEUKEMIAS BASED ON MONOCLONAL ANTIBODY-DEFINED CELL SURFACE ANTIGENS.

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Blood; 59(2):207-215 1982

A panel of monoclonal antibodies reactive with normal lymphocyte subsets was used to classify cases of lymphocytic leukemia on the basis of cell surface antigen expression. The antibodies employed were commercially available and included a common framework HLA-DR antibody, two pan-T antibodies (Leu-1 and OKT-3), and antibodies defining cytotoxic/suppressor (Leu-2 and OKT-8) and helper/inducer (Leu-3 and OKT-4) subpopulations of normal T lymphocytes. Cases of ALL could be subgrouped into non-T non-B, pre-T and T-ALL on the basis of reactivity with HLA-DR, Leu-1, and OKT-3 antibodies. Leukemic cells from patients with T-cell CLL could be divided into Leu-2/OKT-8 reactive and Leu-3/OKT-4 reactive subpopulations, as well as a subgroup in which the majority of cells were unreactive with either of these antibodies. With the exception of one individual, all Sezary cell leukemias expressed a phenotypic pattern similar to that of the Leu-3 subgroup of T-CLL. Malignancies of B-cell lineage (B-CLL, prolymphocytic leukemia, and lymph osarcoma) that were examined were reactive with both the HLA-DR and Leu-1 antibodies. On the contrary, normal B lymphocytes and lymphoid cell lines of B-cell origin did not express surface antigens recognized by the Leu-1 antibody. (Author abstract) (56 Refs)

12. EXPRESSION OF IA-ANTIGENS ON NORMAL AND CHRONIC MYELOID LEUKEMIC HUMAN GRANULOCYTE-MACROPHAGE COLONY-FORMING CELLS (CFU-GM) IS ASSOCIATED WITH THE REGULATION OF CELL PROLIFERATION BY PROSTAGLANDIN E.

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Blood; 59(2):284-292 1982

The presence of Ia-antigens and their relationship to the inhibitory effect of prostaglandin E on the proliferation of human CFU-GM was studied in normals and patients with chronic myeloid leukemia. Consistent reduction of normal colony formation to approx 50% of baseline levels was observed using a monoclonal anti-human Ia antibody in a complement-dependent cytotoxicity assay titrated over serial dilutions. Elimination of the Ia-antigen-bearing CFU-GM population was associated with virtually a complete loss of responsiveness to the inhibitory effect of prostaglandin E. Maintenance of bone marrow cells in short-term suspension culture at 37 C prior to agar culture resulted in the loss of detectable Ia-antigen on the CFU-GM and, similarly, loss of response to prostaglandin. In contrast, most patients with chronic myeloid leukemia showed greatly reduced levels of Ia-antigens on their CFU-GM in fresh marrow together with lack of prostaglandin sensitivity, suggesting a correlation with the abnormal growth regulation observed in these patients. In two chronic myeloid leukemia patients, levels of Ia-antigen higher than that observed in the majority of patients could be detected and correlated with a residual response to prostaglandin E. These results suggest a relationship in normals between the expression of Ia-antigens on CFU-GM and the physiologic response to regulation by prostaglandin E, and a possible mechanism for the aberrant regulatory response in patients with chronic myeloid leukemia. (Author abstract) (41 Refs)

13. IDENTIFICATION OF HUMAN CML TARGETS. HLA-B LOCUS (B12) ANTIGEN VARIANTS DEFINED BY CTL GENERATED BETWEEN B LOCUS-IDENTICAL (B12) RESPONDER-STIMULATOR PAIRS.

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J Immunol; 128(2):949-955 1982

The genetics of human CML targets were studied by seven CTL generated in combinations in which the responder/stimulator difference was limited to one (or two) HLA-A, -B, or -C

antigens. Unstimulated peripheral blood lymphocytes were used as targets. CTL sensitized against antige ns A11, Aw31, or B17 lysed all cells bearing the respective target from a large panel of cells from unrelated individuals. Hence, at least one CTL clone was directed against the HLA antigen molecule. However, all CTL also exerted cross-kill to cells not sharing the stimulating HLA antigen. For two CTL, the target of the cross-kill was not clarified. Five CTL were found where the cross-kill was directed against antigen HLA-B12 (Bw44 and Bw45). All these CTL were generated in R/S pairs identical for B locus antigens (Bw44/Bw35 heterozygotes). The individual CTL lysed different parts of the panel of B12-positive target cells. The interpretation is that these CTL detect subtypes of HLA antigens, but alternative possibilities are also considered. Four B12 subtypes are described, tentatively designated as B12-related CML targets. Identification of HLA-B-related CML targets represent CML 'typing' of HLA-antigenic differences that were not detected serologically. The subtypes can now be tested for their possible functional significance. (Author abstract) (68 Refs)

14. CLINICAL EVALUATION OF NCA IN PATIENTS WITH CHRONIC MYELOCYTIC LEUKEMIA.

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Dept. Virology, Natl. Bacteriological Lab., Stockholm, Sweden
Int J Cancer; 29(2):133-137 1982

NCA, a normal colon and granulocyte antigen, which has been found in large amounts in myelocytes and metamyelocytes and in smaller amounts in neutrophil granulocytes, was studied in 50 CML patients in various stages of the disease. Radioimmunoassay was used to demonstrate NCA in serum. Untreated CML patients had a mean level of 732 ug NCA/l, poorly controlled patients 421 ug/l and well-controlled patients 160 u/l. These values differ significantly from the mean of healthy persons, which was 71 ug NCA/l. The serum NCA levels were related to the number of maturing myeloid cells in blood, and to the clinical course in the chronic phase of CML. In blast crisis low values with a mean of 109 ug NCA/l was found. Patients with ANLL had a low mean level, 50 ug/l. Low levels of NCA could not be attributed to antibodies to NCA. NCA is a normal myeloid differentiation antigen. Despite this, its occurrence in serum in leukemic patients differs from normal. This probably has to do with the abnormal amount as well as the release of NCA by leukemic maturing myeloid cells. (Author abstract) (27 Refs)

15. IMMUNOGLOBULINS IN THE CEREBROSPINAL FLUID OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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Pediatr Pol; 56(9):1053-1058 1981

Immunoglobulin and albumin levels were determined in the cerebrospinal fluid of 15 children (3-7 yr old) with acute lymphoblastic leukemia and of 36 healthy controls. The IgG levels were inc reased in more than 50% of the patients, the albumin levels were increased in 2/15 patients. Trace amount of IgM without increased IgG and albumin levels was found in 1/15 patient. IgA was not found in the cerebrospinal fluid of any of the patients. The mean IgG levels were 1.76 mg% in the patients and 0.94 mg% in the controls; the albumin levels 12.5 mg% and 8.8 mg%, respectively, and the relative IgG levels 16.0% and 10.1%, respectively. All three differences were statistically significant. Increased permeability of the blood-brain barrier for IgG and serum albumin was demonstrated in some of the patients. The possibility of active immune reactions in the nervous system with local production especially of IgG was demonstrated in more than 25% of the patients. (25 Refs) (In POL)

16. IMMUNOLOGICAL DIAGNOSIS OF VARIANTS OF CHRONIC LYMPHOID LEUKEMIA AND LYMPHOSARCOMA.

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Ter Arkh; 53(11):73-78 1981

Diagnostic efficacy of determination of surface immunoglobulins (Ig) was studied in 79 patients with various lymphoproliferative diseases. Surface Ig were studied by direct immunofluorescence assay using conjugated gamma-globulin heterosera against heavy and light chains. FC- and CR2-receptors were studied by indirect rosette-formation assay. On the basis of immunologic phenotyping, the lymphoproliferative diseases were divided into B- and T-cell neoplasms. Analysis of surface markers allowed differential diagnosis within the B-cell and T-cell types of neoplasms. Of 48 patients with chronic lymphoid leukemia (CLL), 46 had B-cell variant. Characteristic features of B-cell variant of CLL consisted of low density of surface Ig, presence of CR2-receptor in 44.5% of the cells, presence of Fc-receptor in 17.1% of the cells, and presence of receptor for mouse RBC in 50.4% of the cells. The B-cell variant of prolymphocytic CLL (1 patient) was characterized by high density of surface Ig, low density of CR2-receptor, and extremely low density or complete absence of receptors for mouse RBC. Hairy cell variant of B-CLL (7 patients) was characterized by the absence of CR2-receptors, presence of Fc-receptor, and low density of receptors for mouse RBC. B-cell lymphosarcomas (20 patients) had surface markers similar to those in CLL. T-cell neoplasms (2 CLL, 2 lymphoblastic lymphosarcomas, and 1 acute lymphoblastic leukemia) showed high densities of receptors for sheep RBC. (21 Refs) (In RUS)

17. THE PRESENCE OF MONOCLONAL CYTOPLASMIC IMMUNOGLOBULINS IN LEUKEMIC B CELLS FROM PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

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Blood; 59(2):435-438 1982

It has generally been assumed that CLL B cells do not contain cytoplasmic immunoglobulin (CyIg), although these cells express surface membrane immunoglobulin (SmIg). The present study, in which SmIg and CyIg determinations were performed simultaneously using leukemic B cells from 20 patients with CLL, demonstrates that CyIg staining was detectable in each CLL cell population examined and that the intensity of cytoplasmic immunofluorescent staining in each instance was moderate to strong. Both SmIg and CyIg light chain determinations indicated monoclonality in all 20 cases. The heavy chain class of SmIg and CyIg in each CLL cell population was not uniformly comparable, however. The majority (15 cases) of CLL B cells contained mu heavy chain CyIg and mu and delta heavy chain CyIg was demonstrated in the remaining six cases. In contrast, the SmIg phenotype appeared heterogenous with both gamma and alpha chain determinants found associated with mu or mu and delta chains on the same leukemic cell populations. This apparent polyclonal SmIg staining pattern

was most likely due to nonspecific adsorption of the patient's own serum Ig by Fc receptors on CLL B cells. It is concluded that the great majority of CLL B cells contain detectable CyIg and that CyIg determination is superior so SmIg phenotyping in documenting the monoclonality of CLL. (Author abstract) (12 Refs)

18. UNUSUAL INTRACYTOPLASMIC IMMUNOGLOBULIN INCLUSIONS IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Guglielmi P, Preud'Homme JL, Gourdin MF, Reyes F, Daniel MT
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Br J Haematol; 50(1):123-134 1982

Unusual intracytoplasmic immunoglobulin inclusions were found by immunofluorescence in three patients with chronic lymphocytic leukemia. The inclusions contained the same immunoglobulin chains as those detected on the plasma membrane, except for delta chains which were expressed on the cell surface and not in the cytoplasmic inclusions. The cytoplasmic staining persisted throughout culture for 8 or more days. An initial study of patient number one's cells showed that the inclusions contained only mu chains, and kappa chains gradually became apparent after in vitro culture. In a second study, the fresh lymphocytes contained both mu and kappa chains. Initially, biosynthetic experiments showed production of mu chains which polymerized in the cytoplasm and were not secreted. Subsequently there was synthesis of heavy and light chains which assembled into monomeric subunits that were retained and secretion of free light chains. The apparent mol wt of these immunoglobulin chains was larger than that of their secretory counterparts. Immunoelectronmicroscopy revealed cytoplasmic mu chains in strands of endoplasmic reticulum. In the two other patients, immunofluorescence displayed unusual staining patterns of bright networks in perinuclear areas. (Author abstract) (31 Refs)

19. IMMUNE COMPLEXES AND CIRCULATING ANTIBODIES AGAINST AUTOLOGOUS LEUKAEMIC CELLS IN PATIENTS WITH ACUTE LEUKAEMIAS.

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Immunology; 45(3):569-575 1982

Serum of patients with different forms of acute leukemias were analyzed either for the presence of circulating antibodies against autologous leukemic cells or for that of soluble immune complexes. At the moment of their diagnosis, 12/25 patients with different types of leukemias, showed circulating serum immunoglobulins capable of binding to the leukemic cell surface (LCS). These anti-LCS immunoglobulins were of the IgG class and were detectable by a binding assay employing glutaraldehyde-fixed target cells and radioiodinated Staphylococcus aureus Protein A. Their digestion with pepsin showed that the site involved in the binding was in the F(ab')2 fragment. The anti-LCS immunoglobulins were observed in patients with non-lymphatic leukemias but not in the four cases of acute lymphocytic leukemia studied. Forty percent of the patients with anti-LCS immunoglobulins had high levels of circulating immune complexes, detectable by a competitive test with bovine conglutinin and an enzymatically-active antigen-antibody probe. After cytostatic chemotherapy, the level of circulating immune complexes decreased in all the patients, while the anti-LCS immunoglobulins remained constantly detectable and appeared also in those who were negative at the day of the diagnosis. (Author abstract) (36 Refs)

20. CELL MEMBRANE MARKERS AND PHYTOHEMAGGLUTININ REACTIVITY OF CIRCULATING LYMPHOCYTES FROM CHRONIC MYELOCYTIC LEUKEMIA PATIENTS.

Rambotti P, Liberati AM, Velardi A, Bellatori E, Martelli MF, Grignani F, Davis S
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Cancer; 49(4):708-713 1982

Lymphocytes from 22 patients with chronic myeloid leukemia (CML), 13 treated with polychemotherapy, 8 by monochemotherapy, and 1 untreated, were analyzed for the presence of classic T and B cell surface markers (E-rosette, EAC-rosette, surface immunoglobulins) and for their ability to respond to phytohemagglutinin (PHA). The absolute number and percentage of E-rosetting cells (T-cells), EAC-rosetting cells and cells staining for surface immunoglobulins (B cells) were all significantly lower than controls (p less than or equal to 0.025). The response to PHA was also significantly lower in patients than in controls at the smaller concentrations of the mitogen (3.75 ug/ml, 30 ug/ml) tested (p less than or equal to 0.01); at a higher PHA concentration (120 ug/ml) the decrease in PHA stimulation approached significance ($p = 0.07$). These lymphocyte abnormalities support the concept that CML lymphocytes may be derived from the leukemic clone. (Author abstract) (21 Refs)

21. SPONTANEOUS MOUSE ERYTHROCYTE-ROSETTE FORMATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Kuhlein E, Laurent G, Rigal F, Delsol G, Pris J, Ducos J
Service d'Immunologie, CHU Purpan, 31052 Toulouse Cedex, France
Clin Exp Immunol; 47(2):389-395 1982

Mouse erythrocyte-rosette-forming cells (MRFC) were determined in 76 cases of chronic lymphocytic leukemia (CLL), 19 cases of centroblastic-centrocytic follicular non-Hodgkin's lymphoma (NHL), 5 cases of hairy cell leukemia (HCL) and in 62 control patients. The mean percentage of MRFC in B-CLL was 54.8% +-24.4%, in nodular centro-follicular NHL 2.3% +-3% in hairy cell leukemia 14.6% +-14.7% and among the controls 3.2% +-1.9%. Thus, MRFC appear to be an excellent marker of B-CLL and sometimes the only B cell marker as in 11 cases of SIg negative CLL. There is no correlation between the percentage of MRFC and clinical staging according to Rai classification whereas patients with Stage 2 in Binet's classification (isolated splenomegaly) have a significantly lower MRFC percentage (23.4% +-27.7%, p less than 0.05). There is no correlation with prognosis, nor with serum Ig levels. We found no correlation with surface phenotype IgM, IgM-IgD or IgG. Thus, this study does not confirm the hypothesis that MRFC might characterize an immature stage in the B lymphocyte differentiation. However, these results are consistent with another hypothesis which states that lymphocytes in CLL possibly originate from a clonal expansion of a normal B lymphocyte subset, characterized by a low concentration of SIg and a receptor for mouse erythrocytes. (Author abstract) (26 Refs)

22. CELL-MEDIATED AND HUMORAL IMMUNITY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Jagielski P, Litwin J, Rokicka-Milewska R, Derulska D, Madalinski K
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Pediatr Pol; 56(9):993-1001 1981

The cell-mediated and humoral immunity was studied in 50 children (2-14 yr old) with acute lymphoblastic leukemia (ALL) during exacerbations and remissions under treatment and in 9 subjects (12-25 yr old) during long-term remission from ALL without treatment. The tests performed included the E rosette test, the spontaneous and phytohemagglutinin (PHA)-, concanavalin A (Con A)- and pokeweed mitogen (PWM)-stimulated blast transformation tests, and the determination of the serum immunoglobulin levels. The E rosette formation was reduced in most patients regardless of the phase of the disease and of the length of treatment. The blast transformation tests were more differentiated: the spontaneous blast transformation of the lymphocytes was increased during the acute phase of the disease, and the PHA-induced blast transformation was decreased during remission. Significant reduction of the blast transformation after stimulation with all three mitogens, and reduced IgA and IgM levels were observed during the second yr of treatment. The only immune deficiency found in the nine patients in long-term remission after withdrawal of the treatment was reduced E rosette formation. (25 Refs) (In POL)

23. ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY OF LEUKAEMIC BLAST CELLS AND NEUTROPHILS FROM PATIENTS WITH ACUTE MYELOGENOUS LEUKAEMIA.

Dallegri F, Holm G, Gahrton G
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Clin Exp Immunol; 47(2):414-418 1982

The antibody-dependent cellular cytotoxicity against ox erythrocytes by blast cells and neutrophils from six patients with acute myelogenous leukemia and one patient with blast crisis of chronic myelogenous leukemia was studied. Leukemic myeloblastic and monocytic cells behaved like potent killer cells toward ox erythrocytes and their activity was comparable with that of neutrophils from leukemic and normal subjects. The target cell destruction was positively related to the effector cell:target cell ratio and was clearly antibody-dependent since the cytotoxic effect did not involve antibody-unsensitized erythrocytes. We suggest that this experimental system, which involves the use of ox erythrocytes sensitized by purified rabbit anti-ox IgG, provides a new and sensitive method for studying antibody-dependent cellular cytotoxicity by myeloid cells. (Author abstract) (11 Refs)

24. GRANULOCYTE AND PLATELET ADHESIVENESS IN MALIGNANT PARAPROTEINAEMIA, LEUKAEMIA AND MYELOPROLIFERATIVE DISEASES.

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Scand J Haematol; 27(5):339-345 1981

Granulocyte and platelet adhesiveness were measured in 36 patients with hematologic diseases, using a glass bead column assay. Platelet adhesiveness (PA) was reduced in malignant paraproteinemia (13/20), leukemia (10/11) and myeloproliferative diseases (3/5). Granulocyte adhesiveness (GA) was reduced in most patients with paraproteinemia and leukemia, but results of measurements in whole blood and in suspensions of leukocytes in autologous plasma were poorly correlated due to the influence of abnormal platelet function and/or concentration on the measurement of GA in whole blood. The results of experiments combining leukocytes and plasma from patients and controls indicte that impaired GA in paraproteinemia is due to a plasma factor, whereas a cellular defect is responsible for the reduced GA in leukemia. (Author abstract) (12 Refs)

CHEMOTHERAPY

25. COMPARISON OF THE THERAPEUTIC RESULTS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA AS A FUNCTION OF THE THERAPEUTIC METHOD.

Derulska D, Rokicka-Milewska R, Skrobowska-Wozniak A, Makowska K, Kansy J
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Pediatr Pol; 56(9):985-992 1981

Three different chemotherapy protocols were compared in the treatment of 111 children with acute lymphoblastic leukemia. Fifty-seven children (Group A: 31 boys and 26 girls, 8 mo to 15 yr old) were subjective to intensive polychemotherapy with vincristine (VCR: 1.5 mg/square meter (m2) 1x/wk) or with VCR and rubidomycin (25 mg/m2 for 4-6 wk) and prednisone (PR: 40 mg/m2/day po) for remission induction. 6-Mercaptopurine (6-MP: 50 mg/m2), methotrexate (MTX: 20 mg/m2/wk) and cyclophosphamide (CP: 200 mg/m2/wk) were administered for maintenance therapy. Cranial irradiation (2,400 rads) and MTX (12 mg/m2 intrathecally) were administered to prevent CNS involvement. The 54 other patients (Groups B and C) were administered less intensive chemotherapy. Thirty-three patients (Group B) were treated with lower doses of PR and VCR than Group A, and with MTX intrathecally to prevent CNS involvement. MTX and 6-MP were administered for maintenance therapy. Group C (20 patients) were treated with PR and 6-MP or MTX for remission induction and with 6-MP and MTX during remission. The remission rates were 98% in Group A, 88.2% in B and 73.3% in C. The 2-yr survival rates were 37% in Group A, 11.8% in B and 0% in C. The 3-yr survival rates were 24% in Group A and 59% in Group B. The duration of the first remission was 14.9 +-10.09 mo in Group A, 7.4 +-4.75 mo in B and 7.95 +-5.34 in C. The length of the first remission in Group A was 6-75 mo. Seven patients in Group A were alive for more than 7 yr at the time of reporting, and five of them were no longer treated. The incidence of CNS involvement was 5.5% in Group A. (28 Refs) (In POL)

26. ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDREN: CURRENT APPROACH IN TREATMENT AND EXPERIENCE AT CHILDREN'S INSTITUTE.

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Pediatr S Paulo; 3(4):296-303 1981

Forty-eight children (22 male, 26 female; 1 mo to 13 yr old) with acute lymphocytic leukemia (ALL_1) were evaluated after receiving protocol VIII of St. Jude Children's Research Hospi-

tal of Memphis, TN. Induction therapy (IT) lasts 28 days and consists of vincristine, prednisone, and L-asparaginase. Prophylaxis therapy of the CNS lasts 2.5 wk and includes cranial radiotherapy (2,400 rad) simultaneously with intrathecal administration of methotrexate (MTX). Maintainance therapy (MT) is administered 30 mo after uninterrupted remission (RE) and consists of 6-mercaptopurine, MTX, and cyclophosphamide. Hemograms were obtained weekly; other tests were performed less frequently. Of seven patients considered to be at high risk, four died due to bronchopneumonia before or during the IT, while three reached RE (1 had RE for 24 wk, followed by septicemia and death; 1 abandoned treatment; and 1, at the time of this report, had been in RE for 22 wk). Of 32 patients considered to be at basic risk, 14 died before or during the IT while 18 achieved RE in 4 wk. Six patients remain in initial remission after 18, 20, 42, 49, 94, and 100 wk. Three patients had relapses and are presently in the MT. Eight patients abandoned the treatment. Treatment of the ALL and selection of proper protocol should be established on a nation-wide basis. (15 Refs) (In POR)

27. MODERATE DOSE METHOTREXATE, VINCRISTINE, ASPARAGINASE, AND DEXAMETHASONE FOR TREATMENT OF ADULT ACUTE LYMPHOCYTIC LEUKEMIA.

Esterhay RJ, Wiernik PH, Grove WR, Markus SD, Wesley MN
Baltimore Cancer Res. Center, Univ. Maryland Hosp., 22 South Green St., Baltimore, MD, 21201
Blood; 59(2):334-345 1982

Thirty-eight adults with acute lymphocytic leukemia (ALL), 24 previously untreated and 14 previously treated, were entered into a study in which sequential, moderate-dose methotrexate and asparaginase were added to vincristine and dexamethasone (MOAD) for remission induction therapy. Eighteen of 24 previously untreated patients (75%) and 11 of 14 previously treated patients (79%) achieved a complete remission (CR). Once in CR, patients were given remission continuation therapy, which included intravenous high-dose methotrexate that was used without prophylactic cranial irradiation and without intrathecal methotrexate because of its potential activity alone as prophylaxis against central nervous system (CNS) leukemia. The median duration of CR was 11.1 mo (range 0.7-55.9+) and median survival 17.0 mo (range 0.4-55.9+) for the 24 previously untreated patients. The median duration of CR was 7.5 mo (range 1.9-55.3+) and median survival 11.2 mo (range 11-55.3+) for the 14 previously treated patients. Only 2 of 24 previously untreated patients (8.3%) developed CNS leukemia at 3.3 and 42.7 mo from start of MOAD. None of the previously treated patients developed CNS leukemia as the initial site of relapse. MOAD is useful as induction therapy for previously untreated adults with ALL, as well as for previously treated patients, and is superior to other regimens that we have used for the treatment of adult ALL. (Author abstract) (52 Refs)

28. TERMINATION OF INTENSIVE POLYCHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Michalewska D, Radwanska U, Duczmal B
I Klinika Chorob Dzieci, Instytut Pediatrii AM, ul. Szpitalna 27/33, 60-572 Poznan, Poland
Pediatr Pol; 56(8):909-914 1981

Intensive maintenance polychemotherapy was terminated after 2.5-3 yr in 72/353 children with acute lymphoblastic leukemia. All patients had been subjected to preventive cranial irradiation. Sixty-two of the 72 patients have remained in first remission: 31 have been in first remission for 5-12 mo, 15 for 12-24 mo, 9 for 24-36 mo, and 7 for more than 36 mo. The 10 other patients (4.3 mo to 10.2 yr) developed recurrence 5-14 mo after the termination of the maintenance chemotherapy. Two of these 10 patients had poor prognosis at the time of diagnosis. The recurrence involved the brain in one patient, the bone marrow in seven, the testicles in one, and the testicles and bone marrow in one. Nine of the 10 patients who developed recurrence were among the 45/72 patients who had been subjected to remission induction therapy with vincristine (VCR) and prednisone (PR), and the 10th patient was one of the 27/72 patients who had been subjected to induction therapy with the combination of VCR, PR and Rubidomycin. Two of the 10 patients achieved second remissions, the two others died. (23 Refs) (In POL)

29. VINCRISTINE AND PREDNISOLONE THERAPY IN BLAST CRISIS OF CHRONIC MYELOGENOUS LEUKAEMIA IN CHILDHOOD.

Kano Y, Takaku F, Sakamoto S, Hida K, Kasahara T, Okamura J, Hasegawa K, Tsukada T, Sasaki H
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Scand J Haematol; 27(5):323-326 1981

Six cases of chronic myelogenous leukemia (CML) blast crisis in childhood were treated with vincristine and prednisolone (V-P). In three terminal transferase (TdT)-positive cases, blast cells were lymphoid in appearance. All three TdT-positive patients entered a complete remission but developed meningeal leukemia. The mean duration of survival from the onset of blast crisis was 32 mo. In three TdT-negative cases, V-P therapy was ineffective. The results of this study suggest that V-P therapy is more effective for CML blast crisis in childhood with TdT positive blast cells and that prophylactic central nervous system treatment is necessary to prevent meningeal leukemia. (Author abstract) (9 Refs)

30. EFFECTIVE MULTIDRUG, MULTIMODALITY CONSOLIDATION THERAPY OF ADULT ACUTE LYMPHOCYTIC LEUKEMIA: A PRELIMINARY REPORT.

Stein RS, Flexner JM, Collins RD
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Cancer; 49(5):846-849 1982

Twelve of 13 adult patients with acute lymphocytic leukemia, acute undifferentiated leukemia, or convoluted T-cell lymphoma (T-cell ALL) who were treated with Adriamycin, vincristine, and prednisone achieved a complete remission. An intensive consolidation regimen was administered. This regimen included Cytosine Arabinoside, L-asparaginase, and multiple courses of CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone). In addition, cranial irradiation and intrathecal methotrexate were administered. By actuarial estimate, 81% of previously untreated patients who achieved a complete remission will remain in remission for more than 2 yr. (Author abstract) (17 Refs)

31. ASPARAGINASE AND METHOTREXATE COMBINATION CHEMOTHERAPY IN RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS.

Yap BS, McCredie KB, Keating MJ, Bodey GP, Freireich EJ
M.D. Anderson Hosp., 6723 Bertner Ave., Houston, TX, 77030
Cancer Treat Rep; 65(Suppl1):83-87 1981

We have treated 37 adults with acute lymphoblastic leukemia (ALL), who have relapsed on previous intensive chemotherapy, with a combination of L-asparaginase and methotrexate (MTX) +- ifosfamide. The initial study included 26 patients who received the two-drug combination of L-asparaginase and MTX given sequentially. Of the 26 patients, 15 (58%) achieved complete remission (CR), while 3 patients had a partial remission (PR), resulting in an overall response rate of 69%. The median duration of CR was 17.5 wk. The median survival of complete responders was 39 wk compared with 10 wk for failures ($p = 0.001$). The regimen was generally well tolerated and it was possible to give MTX doses of up to 400 mg/m2 with minimal myelosuppression, and severe stomatitis was infrequent. A further study involved the use of this regimen combined with ifosfamide in 11 patients. In this continuing study, there were six CR's (55%) and two PR's with an overall response rate of 73%. The median duration of CR was 14+ wk, and the median survival was 40+ wk. Combination chemotherapy with asparaginase and MTX is effective in inducing remission in adults with ALL in relapse. It should now be considered for inclusion as part of induction therapy of previously untreated adults with ALL. (Author abstract) (16 Refs)

32. TREATMENT OF THE BLAST CRISIS OF CHRONIC MYELOGENOUS LEUKEMIA WITH 5-AZACITIDINE AND VP-16-213.

Schiffer CA, DeBellis R, Kasdorf H, Wiernik PH
Baltimore Cancer Res. Center, 22 S Greene St., Baltimore, MD, 21201
Cancer Treat Rep; 66(2):267-271 1982

Twenty-seven patients with chronic myelogenous leukemia in blast crisis were treated with a combination of 5-azacitidine (150 mg/m2/day iv in 3 divided doses x 5 days) and VP-16-213 (75 mg/m2/day x 5). No patient had lymphoid histology, and terminal transferase was not present in the 12 patients tested. One complete and 15 partial responses (58% response rate) were seen, with a median survival of 231 days for responders and 73 days for patients who failed to achieve a partial response ($p = 0.008$). The overall survival was 161 days (range, 20-316+). Moderately severe nausea and vomiting, muscle aches, and mucositis (2 patients) were the major side effects, although toxic effects tended to decrease with subsequent courses and many patients could be treated on an outpatient basis. These results compare favorably with other results in this refractory disorder and suggest that 5-azacitidine and VP-16-213 be studied further, either in higher doses or in combination with other agents, in therapy for chronic myelogenous leukemia in bl ast crisis. (Author abstract) (17 Refs)

33. METHOTREXATE ABSORPTION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Craft AW, Rankin A, Aherne W
Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, England
Cancer Treat Rep; 65(Suppl1):77-81 1981

The absorption of oral methotrexate (MTX) has been studied in 124 children with acute lymphoblastic leukemia (ALL). Blood levels of MTX were very variable and unpredictable. There was a 20-fold difference between the highest and lowest peak level achieved. Division into two groups has shown that those children who absorb MTX slowly have a worse disease-free survival. It is possible that MTX damages the intestinal mucosa and causes a malabsorption of itself in some children. It is suggested that future protocols for the treatment of ALL should include pharmacokinetic studies, which may help to explain the unexpected relapses of good prognosis patients and lead to the development of more effective treatment. (Author abstract) (9 Refs)

34. CYTOSINE ARABINOSIDE INFLUX AND NUCLEOSIDE TRANSPORT SITES IN ACUTE LEUKEMIA.

Wiley JS, Jones SP, Sawyer WH, Paterson AR
Dept. Hematology, Austin Hosp., Melbourne, Australia
J Clin Invest; 69(2):479-489 1982

Although cytosine arabinoside (araC) can induce a remission in a majority of patients presenting with acute myeloblastic leukemia (AML), a minority fail to respond and moreover the drug has less effect in acute lymphoblastic leukemia (ALL). The carrier-mediated influx of araC into purified blasts from patients with AML, ALL, and acute undifferentiated leukemia (AUL) has been compared to that of normal lymphocytes and polymorphs. Blasts showed a larger mediated influx of araC than mature cells. The mean influx for myeloblasts was four-fold greater than the mean for lymphoblasts. The number of nucleoside transport sites was estimated for each cell type by measuring the equilibrium binding of [3H]nitrobenzylthioinosine (NBMPR), which inhibits nucleoside fluxes by binding with high affinity to specific sites on the transport mechanism. Patients with AUL were heterogeneous since blasts from some gave values within AUL myeloblastic range and others within the lymphoblastic range. The araC influx correlated closely with the number of NBMPR binding sites measured in the same cells on the same day. Transport parameters were measured on blasts from 15 patients with AML or AUL who were then treated with standard induction therapy containing araC. Eight patients entered complete remission, while seven failed therapy, among whom were the three patients with the lowest araC influx (less than 0.4 pmol/10(7) cells per min) and NBMPR binding (less than 3,000 sites/cell) for the treated group. In summary, myeloblasts have both higher araC transport rates and more nucleoside t ransport sites than lymphoblasts and this factor may contribute to the greater sensitivity of AML to this drug. AraC transport varied greater than 10-fold between leukemic blasts and normal leukocytes, but transport capacity related directly to the number of nucleoside transport sites on the cell. Finally, low araC transport rates or few NBMPR binding sites on blasts were observed in a subset of patients with acute leukemia who failed to achieve remission with drug combinations containing araC. (55 Refs)

35. RELATIONSHIP OF 5'-NUCLEOTIDASE ACTIVITY AND ANTILEUKEMIC EFFECT IN 2'-DEOXYCOFORMYCIN THERAPY.

Wortmann RL, Holcenberg J, Poplack DG
Rheumatology 10CN, Wood Veterans Admin. Medical Center, Milwaukee, WI, 53193
Cancer Treat Rep; 66(2):387-390 1982

The biochemical mechanism of the therapeutic activity of 2'-deoxycoformycin (2'DCF) was studied in three patients (13-19 yr old) with acute lymphoblastic leukemia (ALL) refractory to conventional chemotherapy. The patients received 22.5 mg/

square meter of 2'DCF, iv, over 30 min. Activities of RBC and lymphoblast 5'-nucleotidase (ecto-5'NT), adenosine deaminase (ADA), and S-adenosylhomocysteine hydrolase (SAHH) were assayed prior to and after the 2'DCF therapy. Pretreatment ecto-5'NT activities were low (less than 0.1 and 0.3 units) in two patients with T-cell ALL and high (32 units) in one patient with null cell ALL. In spite of differences in initial ecto-5'-NT activity, all patients showed a definite response to chemotherapy. The decline in the number of circulating leukemia cells was associated with inhibition of ADA and SAHH activities. The inhibition was more pronounced for RBC than for lymphoblasts. The degree of ADA inhibition was greater than that for SAHH. These findings indicate that ecto-5'NT activity alone can not be used for predicting the response to 2'DCF. (11 Refs)

36. BONE MARROW CELL COUNT PER CUBIC MILLIMETER BONE MARROW: A NEW PARAMETER FOR QUANTITATING THERAPY-INDUCED CYTOREDUCTION IN ACUTE LEUKEMIA.

Hiddemann W, Clarkson BD, Buckner T, Melamed MR, Andreeff M
Medizinische, Universitatsklinik, Westring 3, 4400 Munster, W. Germany
Blood; 59(2):216-225 1982

A new technique is introduced for determining the number of bone marrow cells per cubic millimeter marrow, providing an accurate and objective means for quantitating therapy-induced cytoreduction. The method requires a correction for admixed peripheral blood in bone marrow aspirates to measure the fraction of remaining pure marrow. While cell kinetic differences between blood, aspirates, and biopsies identify the proportion of contaminating blood cells, the ratio of red cell hematocrits in blood and aspirate gives the volume of trapped blood. By combining both procedures, bone marrow cell counts per unit volume pure marrow result (BMC/cu mm BM), which were found highly reproducible. Blast cell counts (BMBC/cu mm BM) were obtained by additional morphological differentiation. BMC and BMBC/cu mm BM were monitored in 16 patients with acute nonlymphoblastic leukemia treated with daunorubicin, cytosine arabinoside, and 6-thioguanine in combination and in 4 patients with end-stage acute leukemias and non-Hodgkin's lymphomas during high-dose thymidine therapy. Total and daily therapy-induced cytoreduction rates were significantly greater (p less than 0.01) in responders than nonresponders to either regimen. Changes in BMC/cu mm BM were also found representative for changes in BMBC/cu mm BM, since the majority of bone marrow cells were blasts. In acute leukemia, BMC/cu mm BM thus provides accurate and objective measurements of treatment efficacy in vivo and after short periods of drug exposure. Differences in cytoreduction rates within the group of responders also suggest possible prognostic implications. (Author abstract) (34 Refs)

RADIOTHERAPY

37. LYMPHOCYTE SUB-POPULATIONS FOLLOWING SPLENIC IRRADIATION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA.

McCann SR, Whelan CA, Breslin B, Temperley IJ
Dept. Clinical Hematology, Central Pathology Lab., St. James's Hosp., James's St., Dublin 8, Ireland
Br J Haematol; 50(2):225-229 1982

Four patients with chronic lymphocytic leukemia were treated with splenic irradiation, 100 rads per wk for 10 wk. No patient had received prior therapy of any kind. All patients showed an excellent clinical response in terms of decrease in lymphocyte count in blood and bone marrow and decrease in lymph node and spleen size. B and T cell populations returned to normal in all patients as did the ratio of TG to TM cells. Two patients showed an increase in IgM levels, but the overall pattern of immunoglobulins showed no consistent change following treatment. No toxicity was incurred during treatment. We conclude that splenic irradiation is a safe and effective treatment for previously untreated patients with CLL and is associated with a return to normal of lymphocyte sub-populations. The role of the abnormal T cell population in the pathogenesis of the hypoimmunoglobulinemia remains unclear. (Author abstract) (16 Refs)

OTHER THERAPEUTIC MODALITIES

38. GLUCOCORTICOID RECEPTOR AND IN VITRO SENSITIVITY TO STEROID HORMONES IN HUMAN LYMPHOPROLIFERATIVE DISEASES AND MYELOID LEUKEMIA.

Nanni P, Nicoletti G, Prodi G, Galli MC, De Giovanni C, Grilli S, Lollini PL, Gobbi M, Cavo M, Tura S
Istituto di Cancerologia, Universita di Bologna, via S. Giacomo 14, 40126 Bologna, Italy
Cancer; 49(4):623-632 1982

The glucocorticoid receptor (GR) quantitation by a whole-cell assay and/or cytosol technique and the in vitro sensitivity to steroids have been assessed in peripheral blood cells from normal donors and patients with chronic lymphatic leukemia (CLL), acute lymphoblastic leukemia (ALL), lymphosarc oma cell leukemia (LSCL), acute nonlymphatic leukemia (ANLL), and chronic myeloid leukemia (CML). Within the lymphoproliferative diseases, ALL cells exhibited the highest GR concentration (regardless of the method used) and the highest in vitro inhibition of spontaneous [3H]thymidine ([3H]TdR) uptake by glucocorticoids. A significant relationship between GR concentration (whole-cell assay) and in vitro sensitivity to dexamethasone was also found. On the contrary, CLL cells presented the highest sensitivity to glucocorticoids in PHA-stimulated cell cultures. Cells from the only two ALL patients who did not undergo a remission after glucocorticoid-inclusive chemotherapy had both the lowest in vitro sensitivity to dexamethasone and the lowest GR concentration with whole-cell assay. Concerning myeloid leukemia, ANLL patients had GR concentrations slightly higher than those found in the ALL group but exhibited the lowest degree of inhibition of spontaneous [3H]TdR uptake by dexamethasone (stimulatory effects occurred in some cases). CML cells exhibited an inhibition degree by in vitro glucocorticoids significantly higher than

that of ANLL cells but not different from that of lymphoproliferative diseases. No clear relationship among GR pattern, in vitro cell sensitivity to glucocorticoids, and clinicohematologic parameters was observed in myeloid leukemia-bearing patients. (Author abstract) (38 Refs)

MULTIMODAL THERAPY

39. PROGRESS IN PREVENTION OF LEUKEMIA SPREADING TO THE CENTRAL NERVOUS SYSTEM IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Pavlovsky S, Garay G, Scaglione C, Fisman N, Dupont J
Departamento de Oncohematologia, Instituto de Investigacion 'Dr. M. R. Castex', Academia Nacional de Medicina, Buenos Aires, Argentina
Bol Acad Nac Med; 59:85-95 1981

Two protocols were evaluated with respect to preventing the invasion of the CNS by leukemia in patients with acute lymphoblastic leukemia. Protocol 10-LLA-72, started in October 1972 and terminated in December 1975, consisted of vincristine (VCR) and prednisone (PRED), with addition of daunomycin when no remission (RE) was obtained with the VCR and PRED. After the patients were in RE for 28 days, radiotherapy (RT: 2,400 rad) was administered during a period of 3 wk, with intrathecal (IT) methotrexate (MTX) and dexamethasone (DMT) twice a wk for five cycles; the patients were then divided in two groups, one (175 patients) receiving IT MTX-DMT every 3 mo, the other (181 patients) serving as a control receiving the IT MTX-DMT. Both groups received 6-mercaptopurine and MTX po as maintenance and VCR-PRED every 3 mo. Protocol 1-LLA-76, started in January 1976 and terminated in December 1978, also was described. Two groups of 18 patients each, one with and the other without RT, both 36 mo after the prevention therapy of CNS and in complete RE, were evaluated neuropsychologically. After the RT and five doses of IT MTX, additional administration of the IT MTX did not decrease the incidence of leukemia in the CNS. No significant difference in results was observed in the patients receiving IT MTX, either with or without RT, but the time of RE was longer in the patients that did not receive the RT. The patients receiving IT MTX and RT showed a significantly higher incidence of changes in cranial computed tomography, psychometry, and intellectual coefficient; these changes were more prominent in children greater than 5 yr old at time of diagnosis. (28 Refs) (In SPA)

40. EFFECT OF CENTRAL NERVOUS SYSTEM RADIOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA ON LYMPHOCYTE SUBPOPULATIONS AND INDICATORS OF LEUKOCYTE MIGRATION INHIBITION IN THE PERIPHERAL BLOOD.

Cesarz-Kruz E, Lukas A, Sroczynska M, Lukas W, Sonta-Jakimczyk D
Klinika Pediatrii, Sl. AM, ul. 3 Maja 13/15, 41-800 Zabrze, Poland
Pediatr Pol; 56(9):1003-1007 1981

The effects of polychemotherapy and prophylactic cranial irradiation (total dose 2,400 rads) on peripheral blood lymphocyte subpopulations and on leukocyte migration inhibition were studied in 17 children (15 mo to 17 yr old) with null-cell acute lymphoblastic leukemia compared with 30 healthy controls. During remission after induction chemotherapy but before cranial irradiation, the percentages of T, B and null cells were 23.70%, 18.58% and 60.60%, respectively, compared with 64.45%, 23.73% and 10.8% in the controls. The decreases in the T and B cell counts and the increase in the null cell counts compared with the controls were statistically significant. The leukocyte migration indices were 0.833-0.938 vs 0.419-0.625 in the controls. After cranial irradiation the percentages of T, B and null cells were 20.25%, 12.5% and 65.10%, respectively, and the leukocyte migration indices were 0.881-0.887. The depressive effect of the irradiation affected mostly the B cells, and caused no significant changes in the leukocyte migration inhibition. (27 Refs) (In POL)

41. NEUROLOGIC SEQUELAE OF METHOTREXATE AND IONIZING RADIATION: A NEW CLASSIFICATION.

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Cancer Treat Rep; 65(Suppl1):89-98 1981

Therapy for prevention of central nervous system (CNS) leukemia has had a dramatic effect on disease-free survival in children with acute lymphoblastic leukemia (ALL). Now, a majority of children may be in complete remission indefinitely, having completed therapy years ago. Unfortunately, some of these long-term survivors have residual neurologic dysfunction, varying a severity from the not uncommon occurrence of mild intellectual deficit to the fortunately rare instance of debilitating leukoencephalopathy. To help identify inciting factors and ultimately render CNS prophylaxis less neurotoxic, this art icle attempts to categorize the types of neurotoxicities reported in patients treated with methotrexate (MTX) and ionizing radiation. A variety of clinical syndromes are described and related temporally to these treatment modalities. Analyzed in this way, combinations including CNS irradiation appear to be the most neurotoxic. The safest methods are the single modalities, of which high-dose iv MTX may be the least neurotoxic. (Author abstract) (30 Refs)

SUPPORTIVE CARE

42. BONE MARROW TRANSPLANTATION IN LEUKAEMIA (REVIEW).

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Dept. Hematology, Universitatskliniken, Kantonsspital Basel, 4031 Basel, Switzerland
Anticancer Res; 1(5):249-253 1981

The procedure of bone marrow transplantation (BMT) in acute leukemia (AL), recent progress, and problems associated with the procedure are discussed. Graft-vs-host disease (GvHD) and interstitial pneumonia (IP) cause 70% mortality within the first 6 mo after BMT in AL; relapses stopped after 2 yr and a plateau lasting from 2 to more than 8 yr was reached when cyclophosphamide and total body irradiation were used. Despite perfect matching of HLA-identical sibling donors, GvHD remains the major problem in allogeneic BMT; 30-70% of patients develop severe GvHD (30% die) and 10-20% develop chronic and often disabling GvHD. Patients with minimal or no GvHD are at higher risk of recurrent leukemia than those with more severe GvHD. Cyclosporin-A (CyA) has been used to prevent severe or chronic GvHD and IP with no increase in relapse rates. BMT should be performed early in the course of acute myeloid leukemia if an HLA-identical or syn-

geneic sibling donor is available; long-term disease-free survival and potential cures are possible in over 60% of these patients. Experience with 11 patients in first remission or chronic phase undergoing BMT with CyA to prevent GvHD and IP demonstrated that 10 survived as complete chimeras with no evidence of leukemia compared with only 3/11 treated in second or later remission or in early relapse. Use of CyA shortened the median hospitalization time after BMT to 28 days and eliminated early mortality. (34 Refs)

43. THYMUS TRANSPLANTATION AFTER ALLOGENEIC BONE MARROW GRAFT TO PREVENT CHRONIC GRAFT-VERSUS-HOST DISEASE IN HUMANS.

Atkinson K, Storb R, Ochs HD, Goehle S, Sullivan KM, Witherspoon RP, Lum LG, Tsoi MS, Sanders JE, Parr M, Stewart P, Thomas ED
Dept. Hematology, St. Vincent's Hosp., Darlinghurst, Sydney NSW 2010, Australia
Transplantation; 33(2):168-173 1982

Seventeen patients, aged 24 to 43 yr and receiving HLA-identical sibling marrow transplants for treatment of acute nonlymphoblastic leukemia (ANL) or aplastic anemia (AA), were given additional transplants of thymic tissue from unrelated donors in an attempt to prevent the development of chronic graft-vs-host disease (GVHD). They were conditioned for grafting with cyclophosphamide alone (AA) or cyclophosphamide and total body irradiation and received methotrexate after marrow transplant. Thymus tissue was given either as cultured fragments without matching recipient and thymidine donor for HLA or as cultured monolayers of thymic epithelial cells that shared an HLA-A and an HLA-B antigen with the recipient. Eight age-matched marrow graft recipients transplanted from HLA-identical siblings for ANL during the same time period, but for whom thymus tissue was not available, served as controls. Thymus transplantation had no adverse effect on marrow engraftment, and there was no infection or hemorrhage at the site of the implant. Short-term complications such as veno-occlusive disease of the liver and acute GVHD were similar in recipients and nonrecipients of thymic tissue as was the incidence of interstitial pneumonia and varicella-zoster infections. Eight patients in the thymic transplant group and four patients in the control group died before 3 mo. Of the evaluable patients, two of five receiving cultured thymic fragments, four of four receiving thymic epithelial monolayer cells, and three of four in the control group developed chronic GVHD. Thus, thymic transplantation as performed in this study did not prevent chronic GVHD. Modifications of the technique have been devised and those currently in use are described. (Author abstract) (21 Refs)

44. A RANDOMIZED STUDY OF THE PREVENTION OF ACUTE GRAFT-VERSUS-HOST DISEASE.

Ramsay NK, Kersey JH, Robison LL, McGlave PB, Woods WG, Krivit W, Kim TH, Goldman AI, Nesbit ME
Dept. Pediatrics, Univ. Minnesota, Mayo Memorial Building, Box 366, 420 Delaware St., S.E., Minneapolis, MN, 55455
N Engl J Med; 306(7):392-397 1982

A randomized trial was conducted comparing the effectiveness of methotrexate (MTX) alone with that of MTX plus antithymocyte globulin (AG) plus prednisone (P) for the prevention of acute graft-vs-host disease (GvHD) after allogeneic marrow transplantation. Twenty-seven patients had aplastic anemia, 17 acute lymphoblastic leukemia, 11 acute nonlymphocytic leukemia, 7 lymphoma, and 5 chronic myelogenous leukemia. Thirty-five patients received MTX alone (15 mg/square meter (m2) on Day 1 after transplantation, 10 mg/m2 on Days 3, 6, and 11, and the same weekly dose until 100 days after transplantation) and 32 received MTX + AG + P (MTX as in the first group; 15 mg/kg of body wt AG on Days 8, 10, 12, 14, 16, 18, and 20, iv; and 40 mg/m2 P, po, on Days 8-20). At 100 days, 79% of patients given MTX + AG + P were free of acute GvHD, compared with 52% of those given MTX alone. Of those with aplastic anemia, 46% treated with MTX alone had acute GvHD compared with 18% treated with MTX + AG + P. Of those with malignant disease, 50% given MTX alone and 23% given MTX + AG + P had acute GvHD. Chronic GvHD occurred in five patients with no history of acute GvHD; three had received MTX alone and two had received MTX+AG+P. Other than treatment regimen, the recipient's age was the only factor associated with acute GvHD; GvHD rarely occurred in children less than 12 yr old. Patients without acute GvHD had significantly better survival than those with acute GvHD. Leukemic relapse occurred in five patients who received MTX alone and in four who received MTX + AG + P. Thus, the addition of AG + P to MTX significantly reduced the incidence of GvHD in these patients. (16 Refs)

45. BONE MARROW TRANSPLANTATION FOR ACUTE LEUKAEMIA AND SEVERE MARROW APLASIA: AN ANALYSIS OF FIVE PATIENTS.

Beard ME, Heaton DC, Hamer JW, Watson J, Fox HW, Crosier PS, Abbott GD
Dept. Hematology, Christchurch Hosp., Christchurch, New Zealand
NZ Med J; 94(693):249-252 1981

Bone marrow transplantations (BMT) were performed in three patients with severe idiopathic aplasia (SIA: 2 males, 1 female; 8-28 yr old) and two patients with acute leukemia [a 15-yr-old male with lymphoblastoid (ALL) and a 20-yr-old female with myeloid (AML)]. Neither leukemia patient was in complete remission at the time of BMT. All donors were HLA A, B, and MLC compatible siblings of the patients. Patients were conditioned with cyclophosphamide, and in two cases with radiotherapy, prior to BMT. Problems during the procedure included mucositis (1 patient), hemorrhagic cystitis (1), gastrointestinal tract toxicity necessitating hyperalimentation (1), and sinusitis, mild asthma, bronchitis, and fatal acute graft-vs-host disease (GvHD) involving the gastrointestinal tract and necessitating hyperalimentation (1). In the latter case, the patient and donor were both positive for hepatitis B antigen, although no activation of the virus occurred. Patients survived for 45 to 640+ days after BMT. Two patients with SIA and one with ALL survived 190+ to 640+ days, all with mild GvHD of the mouth. The 28-yr-old SIA patient who died 45 days after BMT developed acute GvHD involving the gut and leading to perforation and peritonitis. (24 Refs)

46. TOBRAMYCIN VERSUS GENTAMICIN, IN COMBINATION WITH CEPHALOTIN AND CARBENICILLIN, IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION.

Bacigalupo A, Van Lint MT, Volta C, Grazi G, Soro O, Podesta M, Frassoni F, Marmont A
Divisione Ematologia 5/I, Ospedale San Martino, 16132 Genova, Italia
Tumori; 67(6):525-532 1981

Thirty-six patients with severe aplastic anemia or acute leukemia undergoing bone marrow transplantation or intensive hematologic treatments were randomized to receive gentamicin (1 mg/kg/iv q8h) or tobramycin (1 mg/kg/iv q8h) in combina-

tion with carbenicillin (500 mg/kg/day iv in 4 doses) and cephalotin (200 mg/kg/day iv in 6 doses), at the onset of fever during granulocytopenia. Patients in the g entamicin group were treated for a total of 541 patient days (minimum 5, maximum 106), and patients in the tobramycin group for 426 patient days (minimum 9, maximum 48). All patients received oral decontamination, which included the amino glycoside (either gentamicin or tobramycin) given intravenously. This study showed that (1) no patient had an increase in creatinine level above 1.3 mg per cent and no patient developed renal failure, (2) there was no difference between gentamicin and tobramycin in the efficacy of treating febrile episodes and/or major infections, (3) prolonged intravenous administration (up to 48 consecutive days in the tobramycin group and 106 consecutive days in the gentamicin group) was well tolerated and effective in treating fever of unknown origin in granulocytopenic patients: 45 of 72 febrile episodes resolved while the patients had a granulocyte count below 500/mm3. (Author abstract) (13 Refs)

47. AN EMPIRICAL COMBINATION OF ANTIBIOTICS USED IN APLASIAS DURING CHEMOTHERAPY FOR ACUTE MALIGNANT HEMOPATHIES.

Fiere D, Vuvan H, Guyotat D, Ffrench M, Gonnaud P, Extra JM, Imbert C, Coiffier B, Bryon PA, Rebattu P, Viala JJ
Service d'Hematologie, Pavillon E bis, Hopital Edouard-Herriot, place d'Arsonval, 69374 Lyon Cedex 2, France
Sem Hop Paris; 58(3):139-142 1982

Continuous infusion of amikacin, cotrimoxazole and carbenicillin was the second empirically established combination of antibiotics used when fever occurred during the induction phase of chemotherapy in 65 patients (58 acute myeloid leukemias, 5 acute lymphoid leukemias, 2 non Hodgkin lymphomas). Clinical evidence of infection was available in 25 cases and the infection was bacteriologically documented in 19 cases. Therapy was successful in 57 patients (89%). When infection was clinically or bacteriologically documented the success rates were 92 and 82% respectively. The av length of treatment was 10 days. In 25 patients receiving 2 g of amikacin in continuous infusion, the mean serum concentration was 15.9 ug/ml; in 17 patients receiving 3 g, the mean serum concentration was 19.4 ug/ml. (Author abstract) (15 Refs) (In FRE)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

48. FAMILIAL ERYTHROLEUKEMIA: FOUR CASES OF THE DIGUGLIELMO SYNDROME IN CLOSE RELATIVES.

Nissenblatt MJ, Bias W, Borgaonkar D, Dixon S, Cody RP
7 Wirt St., New Brunswick, NJ, 08901
Johns Hopkins Med J; 150(1):1-9 1982

Erythroleukemia was diagnosed in three brothers during a 6-mo period in 1976. A son of one leukemic had died 5 yr earlier with erythroleukemia. First-degree relatives of these men were evaluated in an attempt to identify contributing factors. Twenty-four relatives have been studied. Immunoglobulin M was elevated in 14 of 16 persons (mean, 352.8 mg/dl; normal, less than 145 mg/dl; p less than 0.001). This was neither a monoclonal protein nor rheumatoid factor. Age-dependent red cell enzymes were increased. Erythrocyte hexokinase was markedly increased in 23 of 24 persons (mean, 35.05 units/100 ml RBC; normal, less than 18 units; p less than 0.001). Evidence for a hemolytic state was absent. Bone marrow samples in eight first-degree relatives were normal. Cytogenetics were normal in 18 relatives. One leukemic exhibited hypoploidy and a marker chromosome. The association of an immunoglobulin abnormality and enzymopathy in the leukemics and relatives alike suggests a hereditary susceptibility to the development of erythroleukemia. The exact link is not identified. (Author abstract) (35 Refs)

49. KLINEFELTER'S SYNDROME AND ACUTE NON-LYMPHOCYTIC LEUKEMIA.

Muts-Homsma SJ, Muller HP, Geraedst JP
Dept. Medicine, Div. Haematology, Univ. Hosp., NL-2333 AA Leiden, The Netherlands
Blut; 44(1):15-20 1982

Case reports are presented of five patients (30-64 yr old) with Klinefelter's syndrome (KS) among 51 male adult patients with acute non-lymphocytic leukemia (ANLL). Peripheral blood was cultured for 24 hr without stimulation and for 72 hr in the presence of phytohemagglutinin (PHA). All chromosome analyses were performed after G-banding. All of the patients had a 47,XXY karyotype; one patient showed the same karyotype when bone marrow cells were cultivated with or without PHA stimulation. Cultures of one patient showed three different cell lines, two of which contained acquired chromosome anomalies, +8 and 20 q-,+21. The incidence of KS in this series (1:10) was much higher than that in the combined data of six newborn studies with 35 cases of the KS chromosome abnormality among 37,779 males (about 1:1,000). It is concluded the Klinefelter's syndrome probably predisposes to the development of ANLL, although the causative factor(s) are unknown. (23 Refs)

50. HYPOTHESIS: THE ENVIRONMENT IS A MAJOR DETERMINANT OF THE IMMUNOLOGICAL SUB-TYPE OF LYMPHOMA AND ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN.

Ramot B, Magrath I
Dept. Haematology, Chaim Sheba Medical Centre, Tel Aviv Univ. Medical Sch., Tel Aviv, Israel
Br J Haematol; 50(2):183-189 1982

Based on a study of socioeconomic status, the ratio of leukemia to lymphoma, occurrence of their subtypes, acute lymphoblastic leukemia (ALL) in American blacks, and the early age-peak of ALL, a hypothesis is presented that the pattern of lymphoid malignancy in children is dependent on environment and particularly on socioeconomic circumstances. In the most economically underprivileged, ie in equatorial Africans, B-cell lymphomas predominate, leukemia is rare, and ALL may be entirely of the T-cell type. In populations of intermediate economic status, ie in American blacks and Israeli Arabs, B-cell lymphomas are infrequent and the spectrum of lymphoma varies according to the particular local mosaic of environmental and/or genetic factors. In the highest, socially privileged class, ie American whites and Europeans, ALL has a high incidence and is the most common malignant disease in children. (33 Refs)

SELECTED PRE-CLINICAL STUDIES

51. SELECTIVE KILLING OF LEUKAEMIA CELLS BY ANTIBODY-TOXIN CONJUGATES: IMPLICATIONS FOR AUTOLOGOUS BONE MARROW TRANSPLANTATION.

Krolick KA, Uhr JW, Vitetta ES
Dept. Microbiology, Univ. Texas Southwestern Medical Sch., Dallas, TX, 75235
Nature; 295(5850):604-605 1982

The recent development of tumor-reactive monoclonal antibodies has stimulated interest in their use in targeting toxic agents to tumor cells. One such approach involves the covalent coupling of tumor-reactive antibodies to the toxic peptide of the plant toxin, ricin. Such conjugates are highly effective in killing various tumor cells in vitro. Here we have used the murine B-cell tumor, BCL, in an adoptive transfer system capable of detecting 1-10 tumor cells, to demonstrate the effectiveness and specificity of an anti-immunoglobulin(Ig)-ricin A chain conjugate in deleting tumor cells from infiltrated murine bone marrow. We report that the transferred cells were able to repopulate the hematopoietic system of lethally irradiated mice and that in most mice the tumor did not recur. We discuss the implications of this approach for autologous bone marrow transplantation following supralethal tumor therapy. (Author abstract) (13 Refs)

52. RETINOIC ACID. INHIBITION OF THE CLONAL GROWTH OF HUMAN MYELOID LEUKEMIA CELLS.

Douer D, Koeffler HP
Div. Hematology/Oncology, Dept. Medicine, Univ. California Sch. Medicine, Los Angeles, CA, 90024
J Clin Invest; 69(2):277-283 1982

Vitamin A and its analogues (retinoids) affect normal and malignant hematopoietic cells. We examined the effect of retinoids on the clonal growth in vitro of myeloid leukemia cells. Retinoic acid inhibited the clonal growth of the KG-1, acute myeloblastic leukemia, and the HL-60, acute promyelocytic leukemia, human cell lines. The KG-1 cells were extremely sensitive to retinoic acid, with 50% of the colonies inhibited by 2.4-nM concentrations of the drug. A 50% growth inhibition of HL-60 was achieved by 25 nM retinoic acid. Complete inhibition of growth of both leukemia cell lines was seen with 1 uM retinoic acid. Exposure of KG-1 cells to retinoic acid for only 3-5 days was sufficient to inhibit all clonal growth. The all-trans and 13-cis forms of retinoic acid were equally effective in inhibiting proliferation. Retinal, retinyl acetate, and retinol (vitamin A) were less potent inhibitors. Clonal growth of the human K562 and mouse M-1 myeloid leukemic cell lines was not affected by 10 uM retinoic acid. Retinoic acid also inhibited the clonal growth of leukemia cells from five of seven patients with acute myeloid leukemia. Retinoic acid at concentrations of 5 nM to 0.3 uM inhibited 50% clonal growth, and 1 uM retinoic acid inhibited 64-98% of the leukemic colonies. The inhibition of clonal growth of KG-1 and HL-60 cell lines and of leukemic cells from two patients was not associated with the presence of a specific cytoplasmic retinoic acid-binding protein. Our study suggests that retinoic acid may prove to be effective in the treatment of human myeloid leukemia. (Author abstract) (33 Refs)

53. DEACYLCORTIVAZOL, A POTENT GLUCOCORTICOID WITH UNUSUAL STRUCTURE AND UNUSUAL ANTI-LEUKEMIC CELL ACTIVITY.

Thompson EB, Simons SS, Harmon JM
Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, Bethesda, MD, 20205
Adv Exp Med Biol; 138:315-324 1982

Induction of tyrosine aminotransferase (TAT) and lympholysis of T-derived leukemic lymphoblasts by deacylcortivazol (DAC) were investigated in HTC rat hepatoma cells and CEM-C7 human acute leukemic lymphoblasts. Two toxic effects on lymphoblasts were observed: the classic glucocorticoid effect with high potency and the ability of the compound to kill completely glucocorticoid-resistant clones irrespective of their residual receptor content. DAC was approx 400x more potent than cortisol in inducing TAT. DAC and similar compounds may have chemotherapeutic potential for certain blood dyscrasias. (22 Refs)

54. BONE MARROW TRANSPLANTATION ACROSS MAJOR HISTOCOMPATIBILITY BARRIERS IN MICE. III. TREATMENT OF DONOR GRAFTS WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST LYT DETERMINANTS.

Vallera DA, Soderling CC, Kersey JH
Dept. Therapeutic Radiology, Box 367, Mayo Memorial Building, 420 Delaware St., Southeast, Minneapolis, MN, 55455
J Immunol; 128(2):871-875 1982

We studied the effect of eliminating T cells from donor grafts of mice in a system in which bone marrow was transplanted across major histocompatibility barriers, BALB/c bone marrow (added as a source of hematopoietic stem cells) combined with equal volumes of spleen cells (added as a source of GVHD-promoting cells) was pretreated in vitro with monoclonal anti-Lyt-1.2 or Lyt-2.2 plus absorbed rabbit complement before injection into C57BL/6 total-body-irradiated recipients. Functional activity of anti-Lyt monoclonal antibodies was determined in CML assay. Treatment with anti Lyt-1.2 plus C did not have any anti-stem cell activity, as measured by CFU-S assay, and protected recipients from the onset of lethal GVHD. Treatment with Lyt-2.2 plus C also did not reduce CFU-S; however, mice receiving treated marrow did develop GVHD and were all dead by 2 mo, as were untreated control mice. Surviving 'anti-Lyt-1.2 + C chimeras' demonstrated a high percentage of donor mononuclear cells in their peripheral blood. Similar results were obtained when C3H/HeN donor BMS was treated with monoclonal anti-Lyt-1.1 plus C and injected into C57BL/6 recipients. These findings show that monoclonal antibodies directed against determinants unrelated to Thy-1 can eliminate T cells in the presence of C and successfully protect transplanted mice from lethal GVHD. They also suggest that these anti-Lyt antibodies may be useful tools in determining subpopulations of T cells that contribute to the development of GVHD. (Author abstract) (24 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/121

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Diagnosis, Treatment

SERIES CT03 No. 82/08

AUGUST, 1982

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DIAGNOSIS

1. THE PROGNOSTIC VALUE OF BONE INVOLVEMENT IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

Pastore G, Miniero R, Cordero di Montezemolo L, Felicioni V, Fiandino G, Grazia G, Morgando MP, Trada M, Madon E
(c/o Madon) Clinica Pediatrica E, Universita di Torino, Piazza Polonia, 94, 10126 Torino, Italy
Haematologica (Pavia); 66(6):750-755 1981

Complete skeletal radiographic study was performed in 99 children with acute lymphoblastic leukemia (ALL), 58 of them had no bone involvement (BI), 15 had minimal changes of the bones (localized or diffuse demineralization), and 26 had bone lesions characteristic of the ALL (areas of o steolysis in one or

HE 20. 3173/2:

more skeletal segments). Treatment consisted of different protocols of polychemotherapy. Prophylaxis of CNS was executed with the aid of methotrexate or telecobalt radiotherapy or a combination of both. Distribution of different protocols of polychemotherapy for the treatment of the ALL and prophylaxis of the CNS was evenly divided between the three groups of patients. Nine children with enlarged mediastinum and eight with testicular or ovarian relapse did not show BI at the time of diagnosis. Av duration of complete remission (CR) for the three groups was 42 mo, 39 mo, and 51 mo, respectively Thirty-six mo after diagnosis, 63% of children with BI in less than three bones were in CR, compared with 74% of the children with BI in more than three bones. No correlation was noted between BI and other prognostic factors. (17 Refs) (In ITA)

2. MAJOR BONE LESIONS IN ACUTE LYMPHOBLASTIC LEUKAEMIA.

Hughes RG, Kay HE

Dept. Haematology, The Royal Marsden Hosp., Fulham Road, London, SW3 6JJ, England

Med Pediatr Oncol; 10(1):67-70 1982

The records of 1,471 patients with ALL entered into UKALL trials II-V (1972-1977) were studied, and major bone lesions at diagnosis were recorded in 47 (3.2%). These were found predominantly in young patients (median age 5 yr), equally in both sexes, and were seen to be associated with a low blood leukocyte count and prolonged remissions. (Author abstract) (8 Refs)

3. MYELOFIBROSIS IN ACUTE LEUKEMIA.

Ghandour C, Le Prise P, Ramee M

Clinique Hematologique, CH de Rennes, F-35000 Rennes, France

Nouv Rev Fr Hematol; 23(4):219-225 1981

In 68 adult patients with acute leukemia, the histological changes in bone marrow reticulin (BMR) were studied. A total of 93 bone marrow biopsies were analyzed. In 27 patients, BMR was normal. In 29 patients, myelofibrosis (MF) was in its initial stages. The degree of MF was moderate in 26 patients and intense in 3 of these patients in the initial stages. In cases of initial MF that were followed, complete remission of the leukemia was accompanied by regression of MF. In 45% of the patients with MF, bone pain was experienced as compared to 5% of patients without MF. Dry bone marrow biopsies were observed in 45% of the patients with MF as compared to 8% of the patients without MF. The rate of complete remission of all cytological types of leukemia was not related to MF. The duration of complete remission was slightly longer for the patients with MF. There were no significant differences between the patients with MF and without MF in response to treatment or survival time. (16 Refs) (In FRE)

4. CYTOLOGICAL SUB-CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIAS (FAB SYSTEM). TEST OF REPRODUCIBILITY OF CLASSIFICATION BY A GROUP OF 37 INVESTIGATORS.

Bryon PA, Flandrin G, Sultan C, Amar M, Bayle-Weisgerber C, Bezou M, Bizet M, Bo nhomme J, Bremond JL, Cadiou M, Corberand J, Cosson A, Daniel MT, Delobel J, Falkenrodt A, Felman P, Gentilhomme O, Grange MJ, Horchowski N, Humbert JC, Imbert M, I anys R, Maiel AM, Mater M, Mathiot C, Mayer S, Merle-Beral H, Navarro J, Raphael M, Reiffers J, Sebastion G, Seigneurin D, Sigaux F, Teillet F, Treille-Ritouet M, Valensi F, Vasselon M, Zittoun R

Service d'Hematologie, Faculte de Medecine Alexis-Carrel, Hopital Edouard-Herriot, Pavillon E bis, F-69374 Lyon Cedex 2, France

Nouv Rev Fr Hematol; 23(4):235-241 1981

Sub-classification of FAB system L1/L2 acute lymphoblastic leukemia was studied based on the following criteria: nucleocytoplasmic ratio, nucleolar characteristics, irregularity of nuclear profile, and cellular size. Bone marrow smears from 14 patients were classified by 9 organizers of the meeting and by 28 hematologists who had had a short course on the classification criteria. In the former group, results showed good agreement in 11/14 cases, while in the latter group, good agreement was obtained in only 6/14. The applicability of these classification criteria for widespread use is discussed. Difficulties observed were related to interpretation of certain recommendations (nuclear profile and nucleoli) and problems related to the determination of size and surface characteristics. Morphometric characteristics determined for the 14 smears are compared. (9 Refs) (In FRE)

5. SPLENIC ALTERATIONS IN HAIRY-CELL LEUKEMIA: II. AN ELECTRON MICROSCOPIC STUDY.

Pilon VA, Davey FR, Gordon GB, Jones DB
(c/o Davey), State Univ. New York Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210

Cancer; 49(8):1617-1623 1982

Spleens from nine patients with hairy-cell leukemia (HCL) were studied for ultrastructural alterations. In all cases, hairy cells with typical ultrastructural characteristics were observed within splenic cords and sinuses. Hairy cells had numerous cytoplasmic processes that interdigitated with cytoplasmic processes of other hairy cells. Hairy cells also adhered to sinus endothelial cells and ring fibers and protruded into spaces between endothelial cells. Some normal sinuses were filled with aggregated hairy cells. Other sinuses appeared dilated. Many sinuses were lined by hairy cells that covered thinned endothelial cells and ring fibers. In these abnormal sinuses, endothelial cells were decreased and many appeared injured. The splenic cords were expanded by an infiltration of hairy cells and by large blood-filled spaces. These findings suggest that hairy cells adhere to many cell surfaces, produce endothelial cell injury and death, and impede the venous flow of blood in the spleen. All of the factors appear to influence the formation of the abnormal splenic sinuses and the blood-filled spaces that characterize HCL. (Author abstract) (25 Refs)

6. CLINICAL AND CYTOLOGICAL CHARACTERISTICS OF THE TERMINAL STAGE OF CHRONIC MYELOID LEUKEMIA.

Romanova AF, Klimenko VI, Stakovetskaia ZS, Gaidukova SN
Res. Inst. Hematology and Blood Transfusion, Kiev, USSR

Vrach Delo; (7):32-34 1982

Clinical and cytological features of the terminal stage of chronic myeloid leukemia (CML) were studied in 58 patients

(30 men, 28 women; 23-68 yr old). Duration of the CML was 1-14 yr. All patients received maintenance chemotherapy with myelosan or myelobromol. The terminal stage of the CML was characterized by fever, marked hepatomegaly and splenomegaly, enlargement of the peripheral lymph nodes, and leukemic infiltration of the CNS. Analysis of peripheral blood showed anemia, thrombopenia, and progressive increase in the count of nucleated erythronormoblasts. Leukocytes were characterized by decreases in alkaline phosphatase activity, lipid content, and peroxidase activity. A characteristic feature of the blast crisis of CML was marked polymorphism of blast cells. Duration of the terminal stage of the CML was 3-12 mo. (4 Refs) (In RUS)

7. PATHOLOGICAL CHANGES IN THE ORAL TISSUES IN PATIENTS WITH LEUKEMIA.

Gruszewska-Lewczuk L

Klinika CHirurgii Szczekowej, IS AM, ul. M. Sklodowskiej-Curie 24-a, 15-276 Bialystok, Poland

Czas Stomatol; 34(10):979-985 1981

Pathological changes of the oral mucosa were found in 19/20 patients (13 men and boys and 7 women and girls) who died of acute myeloid leukemia (14), acute lymphocytic leukemia (2), chronic myeloid leukemia (2) or chronic lymphocytic leukemia (2). The most frequent findings were infiltrates composed of immature leukocytes in the submucosa, alveolar process and dental pull. Emboli composed of such cells were present in the blood vessels. Erosions and ulcerations of the covering epithelium were deeper and more extensive over the areas where such emboli were present. (9 Refs) (In POL)

8. LYSOSOMAL ENZYMES IN NORMAL AND LEUKEMIC B LYMPHOCYTES.

Kraaijenhagen RJ, Schipper-Kester GP, Rijksen G, De Gast GC, Staal GE

Unit Medical Enzymology, Dept. Hematology, State Univ. Hosp., Catharijnesingel 101, 3500 CG Utrecht, The Netherlands

Clin Chim Acta; 118(2/3):255-263 1982

Activities of 11 lysosomal enzymes (arylsulfatase A, beta-D-galactosidase, alpha-D-galactosidase, N-acetyl-beta-D-glucosaminidase A, N-acetyl-beta-D-glucosaminidase B, N-acetyl-alpha-D-glucosaminidase, beta-D-glucuronidase (BDG), arylsulfatase B (ASB), alpha-L-fucosidase, alpha-D-mannosidase, alpha-D-glucosidase (ADG), and acid phosphatase (AP)), were compared in total lymphocytes, T and non-T lymphocytes and monocytes from patients with chronic lymphocytic leukemia (CLL) and normal subjects, and the T lymphoblastic cell lines CCRF-CEM and CCRF-HSB-2 and the B lymphoblastic cell lines CCRF-SB and Raji. Except for AP, all enzyme activities were markedly lower in leukemic lymphocytes, which are all B lymphocytes. Activities of BDG and to a lesser extent AP were higher in T lymphocytes, whereas ASB and ADG were somewhat lower, but otherwise there was little difference between T and non-T lymphocytes. Comparison of lysosomal enzyme activities from leukemic B lymphocytes and normal, unseparated lymphocytes seems acceptable for most of the enzymes. With the cell lines, T and B lymphoblasts could not be distinguished enzymatically. Determination of lysosomal enzyme activities may be helpful in diagnosis of CLL. (14 Refs)

9. EXISTENCE OF TARTRATE-RESISTANT ACID PHOSPHATASE ACTIVITY IN DIFFERENTIATED LYMPHOID LEUKEMIC CELLS.

Usui T, Konishi H, Sawada H, Uchino H

First Div. Internal Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan

Am J Hematol; 12(1):47-54 1982

Acid phosphatase (AcP) in neoplastic cells from various lymphoid leukemias was examined. In the cytochemical studies, tartrate-resistant AcP (T-rAcP) activity was observed in the neoplastic cells from well-differentiated lymphoid leukemias such as adult T-cell leukemia (ATL), B-cell chronic lymphocytic leukemia (B-CLL), T-cell chronic lymphocytic leukemia (T-CLL), and hairy-cell leukemia (HCL). T-rAcP activity was also detected in a small number of leukemic cells obtained from T-cell acute lymphoblastic leukemia (T-ALL), while it was not detected in the neoplastic cells from null-ALL, macroglobulinemia, and multiple myeloma (MM). In the electrophoretical studies, fraction 1 (F-1), F-3, F-3b, and F-4 were completely tartrate-sensitive, while F-2 was partially resistant and F-5 was completely resistant. T-rAcP activity (F-5) was observed in ATL cells, B-CLL cells, and HCL cells, while it was not detected in ALL cells, macroglobulinemia cells, and MM cells. The present study indicates that T-rAcP activity is observed not only in HCL cells but also in the well-differentiated lymphoid cells such as ATL cells, B-CLL and T-CLL cells except the most highly differentiated forms of B-cells of MM and macroglobulinemia. (Author abstract) (21 Refs)

10. TETRAHYDROFOLATE DEHYDROGENASE CYTOCHEMISTRY AND CLASSIFICATION OF ACUTE LEUKAEMIA.

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Acta Haematol (Basel); 67(3):160-165 1982

Bone marrow and blood smears from patients with acute lymphoblastic and myeloblastic leukemia prior to therapy were stained for tetrahydrofolate dehydrogenase. Compared with other cytochemical tests this reaction seems to discriminate clearly between cells with myeloid and lymphoid features. Lymphoblasts were intensely positive, the reaction being located asymmetrically on one pole of the cell, while myeloid malignant cells were slightly positive with evenly diffused granules in the cytoplasm. Thus, tetrahydrofolate dehydrogenase reaction should be an effective marker of blast cells indistinguishable by other characteristics, as found in unclassifiable leukemia. (Author abstract) (20 Refs)

11. BEHAVIOUR OF TWO SECOND MESSENGERS: CAMP AND CGMP IN LEUKOCYTES OF PERIPHERAL BLOOD OF NORMAL AND LEUKEMIC SUBJECTS.

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Haematologica (Pavia); 66(6):721-732 1981

Cyclic AMP (cAMP) and cyclic guanosine monophosphate (cGMP) were determined in the peripheral blood of 10 healthy controls, of 5 patients with chronic myeloid leukemia (CMA), of 5 with acute myeloblastic leukemia (AML), of 5 with chronic lymphatic leukemia (CLL), and of 5 with acute lymphoblastic leukemia (ALL), using a new radioimmunoassay. Comparing values of normal granulocytes with those for leukocytes of CML and AML, cAMP was decreased by 12% and 88%, re-

spectively, and cGMP was decreased 34% and 62%, respectively. If the values of normal granulocytes, were compared with those for leukocytes of CLL and ALL, cAMP was decreased 68% and 59%, respectively, while cGMP was increased 24% in CLL, and decreased 23% in ALL. cAMP and cGMP were consistently decreased in acute leukemias (AML and ALL) and in CML. The ratio of cAMP/cGMP was similar for the two acute leukemias and quite different for the two chronic leukemias, especially for CLL. Possible causes for such behavior were considered. (52 Refs) (In ITA)

12. 2' AND 3' RIBONUCLEOSIDE MONOPHOSPHATE IN LEUKOCYTES OF ACUTE MYELOID LEUKEMIA: MARKERS FOR EARLY DIAGNOSIS OF RELAPSE.

Scavennec J, Cailla H, Gastaut JA, Maraninchi D, Carcassonne Y
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Int J Cancer; 29(3):257-259 1982

Levels of 2' and 3' purine and pyrimidine ribonucleoside monophosphates (2'-, 3'-NMP) in leukocytes from blood and/or bone marrow were measured in three adult patients with acute non-lymphoblastic leukemias. The measurements of 2'-, 3'-NMP were made by high-performance liquid chromatography (HPLC) at various times in the course of the disease. Complete remission (CR) was obtained for all three patients but two of these have since died after relapsing at 8 and 9 mo, respectively. The third patient remains in CR at 1.5 yr. The levels of 2'-, 3'-NMP in the leukocytes of the patient remaining in remission have not changed since the beginning of his remission. However, in the patients who relapsed 2'- and 3'-NMP levels increased first in bone marrow then in blood leukocytes. These increases occurred about 3 mo before the relapse was detected by morphological criteria. These data suggest that 2'-, 3'-NMP measurements may have a prognostic value if used to monitor patients with acute myeloid leukemia in CR. (Author abstract) (16 Refs)

13. PURINE AND PYRIMIDINE RIBONUCLEOSIDE MONOPHOSPHATE PATTERNS OF PERIPHERAL BLOOD AND BONE MARROW CELLS IN HUMAN ACUTE LEUKEMIAS.

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Cancer Res; 42(4):1326-1330 1982

Purine and pyrimidine ribonucleoside monophosphate (NMP) levels were measured in blood and/or bone marrow cells of groups of patients with acute leukemia including acute lymphoblastic leukemia (ALL) and acute nonlymphoblastic leukemia (ANLL). Patients were either untreated or in remission. Three relapsed patients with ALL were also studied. Phytohemagglutinin-stimulated tonsil lymphocytes and bone marrow cells both from normal subjects were used as controls. Moreover, observations in acute leukemias were compared with those in chronic leukemias. The cytidine, adenosine, guanosine, and uridine 2'-, 3'-, and 5'-monophosphate contents were measured by high-performance liquid chromatography. 2'- and 3'-NMP concentrations were 2.5x higher in ALL and were 5.5x higher in ANLL leukemic cells than in chronic leukemic blood cells or control bone marrow cells. 2'-NMPs were found only in leukemic blast cells and accounted for about 30% of 2'- and 3'-NMP mixtures. Levels of 2'- and 3'-NMP were around two- and four-fold higher in bone marrow than in peripheral blood cells of patients. The high level of 2'- and 3'-NMP found in bone marrow and blood cells of untreated ALL patients decreased during remission without reverting to normal; however, in relapse, it was 5 to 10x higher than in the case of untreated patients. The 5'-NMP concentrations were always lower than those of 2'- and 3'-NMP and were the same in acute leukemias and controls. Furthermore, 5'-NMP levels remained constant during the course of the disease. 2'- and 3'-NMP levels appear therefore to be useful markers of leukemic blasts and may facilitate both the diagnosis of acute leukemia and the monitoring of chemotherapy. (24 Refs)

14. SERUM FERRITIN DURING THE COURSE OF CHRONIC MYELOID LEUKEMIA. INCREASE OF SERUM FERRITIN AS A MARKER OF DYSERYTHROPOIESIS.

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Acta Haematol (Basel); 67(3):145-149 1982

A solid-phase immunoradiometric assay for serum ferritin has been developed and applied to 30 patients with chronic myeloid leukemia (CML), including 13 patients with a typical chronic phase, 12 with bone marrow fibrosis without evidence of an acute phase and 5 with an acute phase. Patients were divided into three subgroups according to the erythrokinetic data as studied by the 59iron kinetic test. Serum ferritin was clearly correlated with the quality of erythropoiesis but not with blast cell mass nor white cell count. Given the prognostic value of dyserythropoiesis in the course of CML, serum ferritin determination may be a helpful and simple parameter in the follow-up of CML patients. (Author abstract) (21 Refs)

15. DECREASED ACTIN CONTENT OF LYMPHOCYTES FROM PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

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Blood; 59(3):536-541 1982

Actin, a major cytoskeletal protein, was quantitated in normal and chronic lymphocytic leukemia lymphocytes. The actin content of normal human blood lymphocytes was 2.2 +-0.4 mg/10(9) cells and represented 6.6% +-1.8% of the total cellular protein. A significant decrease (p less than 0.001) was noted in chronic lymphocytic leukemia lymphocytes that contained 1.4 +-0.3 mg actin/10(9) cells, constituting 4.3% +-1.1% of the total protein. Normal T and B cells did not differ in actin content. Reduced actin levels were found in the T as well as in the B lymphocytes of 'B-cell' chronic lymphocytic leukemia. The possible importance of the decreased actin level in the anomalous capping response and motility of chronic lymphocytic leukemia lymphocytes is discussed. (Author abstract) (54 Refs)

16. READILY EXTRACTABLE NONHISTONE PROTEINS IN NORMAL CHROMATIN AND IN CHROMATIN OF THE PATIENTS WITH DIFFERENT VARIANTS OF LEUKEMIA.

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Medical Inst., Riga, USSR
Eksp Onkol; 4(1) 32-35 1982

The results of comparative analysis of nonhistone proteins extracted with 0.35 M NaCl (0.35 NHP) from granulocytes of healthy donors and from peripheral blood leukocytes of acute leukemia (AL) patients are reported. The total content of 0.35

NHP in the granulocytes was significantly lower than that in the leukocytes of the patients with lymphoblastic and myeloblastic variants of AL. Electrophoresis in polyacrylamide gel showed that 0.35 NHP from normal granulocytes consisted of 18-20 fractions, compared with 22-27 fractions in AL. The patients with myeloblastic AL showed increase of the fractions with intermediate and low electrophoretic motility, while the patients with lymphoblastic variants of AL showed increase of the fast fractions. (26 Refs) (In RUS)

17. PROGNOSTIC SIGNIFICANCE OF BONE MARROW CELL DNA HISTOGRAMS IN ACUTE MYELOBLASTIC LEUKEMIA.

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Acta Haematol Pol; 12(3/4):171-174 1981

The prognostic value of bone marrow cell DNA histogram was studied in 25 adult patients with acute myeloblastic leukemia before treatment. The percentage of myeloblasts in the bon e marrow was above 80% in all patients. Ten of the 25 patients (3 men and 7 women, 19-43 yr old) subsequently achieved complete remissions after polychemotherapy, the other 15 (10 men and 5 women, 15-69 yr old) did not. The percentage of cells in phase S of the cell cycle was significantly higher before treatment in the patients who achieved complete remissions (22 +-3%) than in those who did not (12 +-4%; p = 0.05). The percentages of cells in phases G0 and G1 of the cell cycle were 78 +-3% in the patients who achieved remission, and 88 +-4% in those who did not. The findings indicate that the DNA histogram of bone marrow cells may be one of the prognostic factors in patients with acute myeloblastic leukemia. (11 Refs) (In POL)

18. CYTOGENETIC STUDIES IN PRELEUKEMIC STATES.

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Medicina (B Aires); 41(Suppl):179-186 1981

Chromosomal studies were evaluated for diagnosis and especially for prognosis of preleukemic states. Patients without previous treatment and without clinical or hematologic symptoms of leukemia included 20 patients with refractory anemia (RA), 7 with sideroblastic anemia (AS), 21 with polycythemia vera (PV). Ten patients with ferropenic anemia served as controls, because they have normal karyotypes. Of the 21 patients with PV, all had numerical cytogenetic alterations (CA) and in 17 they were associated with structural alterations (SA), but 15 were in good condition and 5 were stationary. Seven patients with AS had numerical CA; in two they were associated with SA; one of them with 7q developped acute myeloblastic leukemia (AML), the other was stationary, while five were in good condition. Of the 20 patients with the RA, 4 had polyploidy, 3 had diffuse chromosomes (DC), the rest had numerical CA associated in two of them with SA. The two patients with RA died without developping leukemia, one with DC and the other with CA associated with SA (r and 2q +). Four or the patients with RA developped AML, four were in poor condition, one was stationary, and nine were in good condition. Anomalous clones in cytopenic states indicate bad prognosis (high risk for leukemia or short survival), but they are not indicating for PV. (42 Refs) (In SPA)

19. CYTOGENETIC STUDIES USING HPCM-STIMULATED SHORT-TERM LIQUID CULTURES OF CIRCULATING HEMOPOIETIC PRECURSOR CELLS IN PATIENTS WITH MYELOFIBROSIS.

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Blut; 44(2):111-114 1982

Cytogenetic studies were performed on nine patients (5 men, 40-62 yr old and 4 women, 54-70 yr old) with myelofibrosis. Two men and one woman showed signs and symptoms of acute leukemia . Mononuclear cells were separated from samples of peripheral blood and cultured in medium conditioned with fresh human placenta (HPCM). Metaphase preparations were made after 2 days of incubation. Two patients showed evidence of chromosomal abnormalities. All metaphases in cell cultures from one patient with acute myeloid leukemia showed the loss of the Y chromosome. Cell cultures from a patient not showing signs of leukemia showed an abnormal stem line with alterations of chromosomes 7 and 9 (46,XX,7q-,-9,+mar). Results indicate that culturing of hematopoietic cells in HPCM is suitable for determining whether myeloproliferative syndromes are the result of autochthonous proliferation and differentiation of stromal cells or of irreversible abnormalities of hematopoietic stem cells. Detection of abnormal clones indicates that myelofibrosis is a secondary effect of a neoplastic disorder. Absence of abnormal clones does not, however, rule out a leukemic process. (16 Refs)

20. PROGNOSTIC SIGNIFICANCE OF CYTOGENETICAL STUDIES IN CHRONIC GRANULOCYTIC LEUKAEMIA.

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Scand J Haematol; 28(1):77-81 1982

In a series of 121 patients with chronic granulocytic leukemia (CGL) the frequence and prognostic significance of two cytogenetical features (absence of Ph'-chromosome and presence of Ph'-mosaicism) were studied. Thirteen percent of the patients were Ph'-negative, these patients showing a shorter survival than the Ph'-positive ones (p less than 0.005). Twenty three instances of Ph'-mosaicism were found (22.5%). This feature was observed either at diagnosis or after treatment, and irrespective of the patient's being in chronic or blastic phase of CGL, but in no case later than 2 yr from diagnosis of the disease. Ph'-mosaicism patients vs the remainder of the Ph'-positive group were compared for survival, and no difference was found. The lack of prognostic significance of Ph'-mosaicism was evident regardless of the latter feature being detected at diagnosis or after treatment. (Author abstract) (15 Refs)

21. IN VITRO COLONY STUDIES IN 87 PATIENTS WITH ACUTE NONLYMPHOBLASTIC LEUKEMIA: PROGNOSTIC VALUE OF COLONY-STIMULATING ACTIVITY AND COLONY-FORMING CELLS.

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Acta Med Scand; 211(3):195-201 1982

Colony-forming cells (CFU-C) in peripheral blood and bone marrow and colony-stimulating activity (CSA) in mononuclear peripheral white blood cells were studied at diagnosis in 87 patients with acute nonlymphoblastic leukemia (ANLL). Absence of CFU-C in peripheral blood was more frequent in patients

who did not enter remission than in those who did, and survival was significantly shorter in CFU-C negative than in CFU-C-positive patients. No correlation was found between CFU-C in the bone marrow and frequency of remission or survival time. Absence of CSA was significantly more frequent in patients who did not enter remission than in those who did. Only 4 of 28 patients who lacked CSA entered remission. Survival was significantly longer in CSA-positive than in CSA-negative patients. Thus, CSA synthesis in peripheral mononuclear blood cells appears to be a valuable prognostic factor in ANLL. (Author abstract) (36 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

22. IDENTIFICATION AND PARTIAL CHARACTERIZATION OF SPECIFIC ANTIGEN ON ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN.

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Mie Med J; 31(1):57-65 1981

Identification and partial physical and chemical characterization of tumor-specific antigen (TSA) associated with acute lymphoblastic leukemia (ALL) are reported. Peripheral blood samples were obtained from patients with clinically and cytologically diagnosed ALL upon admission to the hospital. Cells were classified as T cell, B cell, or non-T non-B ALL. Also studied were Molt-4B (T cell ALL) and Raji (B cell ALL) cell lines. Rabbit antisera were raised against ALL cells and purified. In indirect immunofluorescence tests, the rabbit antisera reacted with 34/37 non-T non-B samples, 1/4 T cell samples, and no B cell, acute myeloblastic leukemia, chronic lymphoblastic leukemia, chronic myeloblastic leukemia, or Molt-4B samples. The antisera did not react with fetal thymocytes, fetal bone marrow, cord blood, neuroblastoma cells, or normal bone marrow cells. TSA from leukemic cells was extracted by the 3 M-KCl method. In immunoprecipitation tests antiserum reacted with a component of mol wt of 80,000-90,000 daltons. Extracts from non-ALL cells did not react with antisera. The isoelectric point of the TSA was pH 4-5. Results indicate that non-T non-B and a limited number o T cell ALL have a TSA of mol wt 80,000-90,000 daltons. (18 Refs)

23. SURFACE MARKERS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

Liang DC, Hsieh KH, Lin KS
Dept. Clinical Pathology, Coll. Medicine, Natl. Taiwan Univ., Taipei, Taiwan, Republic of China
Taiwan I Hsueh Hui Tsa Chih; 80(11):1160-1168 1981

Sixty-one childhood acute lymphoblastic leukemia (ALL) patients were studied, and the correlation between the immunological classifications and clinical features was explored. Patients with more than 85% of lymphoblasts (LB) in their peripheral blood and/or bone marrow were included in the study. Patients received chemotherapy, and after complete remission most received craniospinal irradiation. Two patients with 85% LB were negative for erythrocyte (E) and erythrocyte antibody complement (EAC) surface markers. Among the other 45 patients with bone marrow checked, 6 were E+ALL, 1 was EAC+ALL, and 38 were E-, EAC-ALL. Among nine early cases of ALL, eight were E-, EAC-ALL. For the deceased six patients with E-, EAC- surface markers, the survival was 18-84 mo (mean 45 mo, median 44.5 mo). Among 36 patients entered later (EL) into the study, 6 were E+ALL and 30 E-, EAC-ALL. The initial clinical features of EL patients are shown. Comparison of 6 E+ and 30 E-, EAC- cases, respectively, showed that median age of onset was 10 and 6 yr, male to female ratio was 5:1 and 14:16, white counts greater than 20 x 10(3) cubic mm in the former and less than 20 x 10(3) cubic mm in the latter, and 4 mediastinal involvements in the E+ group compared with 1 in the E-, EAC-group. Actuarial curves of EL are presented. The E+ group had higher mortality rate (66.6%) and shorter duration of survival (median 7.0 mo, mean 9.0 mo) than the E-, EAC-group. Results indicate that ALL is a heterogeneous disease with respect to clinical characteristics and prognosis. (39 Refs)

24. SURFACE MARKERS ON LEUKEMIC BLASTS AND THEIR PROGNOSTIC SIGNIFICANCE.

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Medicina (B Aires); 41(Suppl):109-117 1981

A retrospective analysis of surface markers (SM) on bone marrow lymphoblasts from 148 patients (1 mo to 39 yr old) with untreated acute lymphoblastic leukemia (ALL) is reported; tests were on cells obtained by bone marrow aspiration at the time of initial diagnosis. Determination of SM included testing for receptors for sheep erythrocytes at 4 C (E4) and 37 C (E37), complement (C3), mouse erythrocytes (ME), and surface immunoglobulins (sIg). Seventy-one percent of the patients had no SM studied. Of the remaining 43 patients, 24 showed only one SM and 19 had two or more: the patients were subdivided into four different groups. T-ALL included E4 or E37 and/or C3, B-ALL included C3 and sIg, C3-All had only C3, and ME-ALL had only ME. T-ALL was predominant in boys greater than 5 yr old with high WBC, while C3-ALL prevailed in girls with WBC less than 50,000/cubic mm. Patients without markers were evenly divided between the sexes; 56% were 5 yr old or less, and WBC was 50,000/cubic mm or less. The relationship between SM and response to treatment, aggressivity, duration of remission, clinical features, and prognosis are analyzed. (45 Refs)

25. TWO MONOCLONAL ANTIPLATELET ANTIBODIES AS MARKERS OF HUMAN MEGAKARYOCYTE MATURATION: IMMUNOFLUORESCENT STAINING AND PLATELET PEROXIDASE DETECTION IN MEGAKARYOCYTE COLONIES AND IN IN VIVO CELLS FROM NORMAL AND LEUKEMIC PATIENTS.

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Blood; 59(3):514-521 1982

Two monoclonal anti-human platelet antibodies have been used in an immunofluorescent assay to study megakaryocyte maturation. The two antibodies were specific for platelets and megakaryocytes. AN 51 recognizes an antigen on platelet glycoprotein Ib, the antigen detected by J 15 is on the glycoprotein IIb/IIIa complex, since it does not bind to platelets from patients with Glanzmann's thrombasthenia. AN 51 did not stain small cells of normal bone marrow, but it labeled most of the megakaryocytes and all of the platelets. In megakaryocyte colonies, megakaryocytes that had reached full maturity (at day 12 of culture) were stained specifically. AN 51 also labeled

micromegakaryocytes (small mature megakaryocytes) in fetal or neonatal cultures and in leukemias, but could not be applied to identification of most leukemia promegakaryoblasts. In contrast, J 15 labeled all megakaryocytes in bone marrow as well as some rare small cells. These cells appear to represent an early cell of the megakaryocyte lineage, since their number was increased in autoimmune thrombocytopenia and they were present as early as the 6th day of culture of megakaryocyte colonies. The size of these cells progressively increased as the culture aged, probably due to endoreplication. In the bone marrow of three patients with leukemias in which promegakaryoblasts were identified ultrastructurally by the presence of platelet peroxidase, J 15 labeled blast cells. Thus, glycoprotein Ib is progressively expressed during megakaryocyte maturation, but its expression is independent of megakaryocyte ploidy, while the glycoprotein IIb/IIIa complex is an early antigenic marker of megakaryocyte maturation that may be useful in isolation of megakaryocyte precursors and diagnosis of megakaryoblastic leukemia. (Author abstract) (32 Refs)

26. MONOCLONAL ANTIBODY AGAINST A MEMBRANE ANTIGEN CHARACTERIZING LEUKEMIC HUMAN B-LYMPHOCYTES.

Forster HK, Gudat FG, Girard MF, Albrecht R, Schmidt J, Ludwig C, Obrecht JP

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Cancer Res; 42(5):1927-1934 1982

In the diagnosis of non-Hodgkin's lymphomas, the ready characterization of the neoplastic cell lineage by analysis of cell surface markers is of great importance. We present evidence for the existence of a human B-leukemia-associated antigen recognized by a complement-fixing monoclonal antibody (anti-Y 29/55). A hybridoma was produced by fusing mouse myeloma cells and splenocytes of a mouse immunized against lymphoid cells of a patient with B-cell chronic lymphocytic leukemia. Characterization of anti-Y 29/55-reactive normal and malignant leukocytes was demonstrated by cytolysis and indirect immunofluorescence. This revealed reactivity with an antigen on B-lymphoma cells (11 patients), on leukemic lymphocytes in B-cell chronic lymphocytic leukemia (13 patients), and on malignant cells in hairy-cell leukemia (2 patients) but not on leukemic cells of T-cell acute lymphoblastic leukemia (1 patient), on T-lymphoma cells (1 patient), on cells of acute myeloblastic leukemia (4 patients), or of chronic myeloid leukemia (4 patients). No specific cytolysis occurred with B- and T-peripheral blood lymphocytes from (a) healthy donors (16 individuals), (b) patient with reactive lymphocytosis (1 patient), (c) nonleukemic multiple myeloma (6 patients), or (d) Hodgkin's disease (3 patients). Surface immunoglobulin-positive, sheep RBC-negative lymphocytes isolated from human spleen (3 individuals), tonsils (7 individuals), and lymph nodes (1 individual), however, we recognized. It is concluded that leukemic B-cells carry a marker characteristic of nonrecirculating sessile B-lymphocytes. (Author abstract) (54 Refs)

27. COMPARISON OF CURRENTLY AVAILABLE MONOCLONAL ANTIBODIES WITH CONVENTIONAL MARKERS FOR PHENOTYPING OF ONE HUNDRED ACUTE LEUKEMIAS.

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Blut; 44(2):95-100 1982

Monoclonal antibodies (mAbs) were compared with conventional antisera for phenotyping acute leukemias. One hundred frozen bone marrow samples were tested. All had been obtained at the time of diagnosis from children with acute leukemia. Samples were typed by reaction with conventional antibody preparations including sheep RBC receptor, surface immunoglobulins, rabbit anti-common acute lymphoid leukemia (anti-cALL) serum, rabbit anti-thymocyte/T cell serum, and rabbit anti-granulocyte serum against myelomonocytic antigens. Fifteen mAbs were tested. VIL-A1 mAbs, directed against the cALL antigen, reacted like rabbit polyclonal antibody in 95/100 serum samples. Other mAbs reacted with considerable heterogeneity. Those mAbs directed against T-cell antigens were capable of classifying subgroups of leukemias according to the degree of T-cell maturation. Detection of OKM1 antigen was indicated as a possible means of diagnosing acute myelomonocytic leukemia. All 'pan-T' mAbs failed to detect some individual samples tested, although general reactive patterns were strong. Diagnostic use of mAbs will require selection of mAbs that react with essential epitopes. (15 Refs)

28. THE PHENOTYPE OF THE NEOPLASTIC CELLS OF HAIRY CELL LEUKEMIA STUDIED WITH MONOCLONAL ANTIBODIES.

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Blood; 59(3):609-614 1982

Eighteen cases of hairy cell leukemia were studied with a battery of polyclonal anti-Ig and nine monoclonal antibodies to determine the lineage of the hairy cells (HC) and the stage of their maturation arrest. Hairy cells tend to nonspecifically bind many antisera and precautions had to be taken to avoid nonspecific fluorescence of the cells. All but one case was reactive with one light chain type and one or more heavy chain isotype antisera as reported before. All cases studied were positive for monomorphic HLA-DR determinants, using monoclonal antibody 7.2. Most cases tested (6/7) were positive with the B-lineage related antibody PI 153/3. While most cases (15/18) were nonreactive with the B-lineage related antibody BA-1, they became positive (5/5) following in vitro culture. Seven out of nine cases were reactive with OKM1. Common acute lymphoblastic leukemia antigen (CALLA) was absent in all (15) cases tested and the ALL associated structure p24/BA-2 was absent from 16 of 18 cases. HC from none of the cases were clearly positive with the T-cell antibodies 9.6, or TA-1, whereas in only 1/18 the cells reacted with T101. The results of this study support the B cell lineage of most HC, and show the presence of multiple phenotypes. In combination with the surface Ig present on the cells, a hierarchy of phenotypes is postulated, with SIgormudelta, BA-1+, PI 153/3+, HLA-DR+ being the most immature, and SIg(alpha)gamma, BA-1-, PI 153/3-, HLA-DR+ the most mature. (Author abstract) (35 Refs)

29. PHENOTYPE CHARACTERIZATION OF CHRONIC LYMPHOCYTIC LEUKEMIA WITH MONOCLONAL ANTIBODIES AND SURFACE RECEPTORS.

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Medicina (B Aires); 41(Suppl):123-130 1981

Different immunologic and enzymatic techniques as well as monoclonal antibodies (MA) were used in 33 patients (21 men, 12 women; 42-84 yr old) with chronic lymphocytic leukemia. Analyses were performed when WBC was greater than 10,000/mm square. T cell markers were determined with sheep red blood cell rosette test (E4 and E37). B cell markers were determined using mouse red blood cell rosette formation test (ER). C3 serum complement was determined by erythrocyte antibody complement (EAC) rosette test. Cell surface (sIg) and cytoplasmic (cIg) immunoglobulins were determined by immunofluorescence. Surface antigens T1, T3, T4, T6, T8, T9, T10, T11a, Ia1, and M1 were evaluated with MA of OK series. All the patients had phenotype B and were divided into four groups (early, immature, immature, mature, and very mature). EAC was present in all the patients, and only 1/3 had ER values greater than 20%. Range of values was 0-37% for E4, 0-27% for E37, 22-94% for EAC, and 0-82% for ER. Results of monoclonal antibodies were positive in 11/12 patients for Ia1, in 7/12 for T1, and in 2/12 for T10, all the others were negative. (16 Refs) (In SPA)

30. STUDIES ON THE ABILITY OF MONOCLONAL ANTIBODIES TO SELECTIVELY MEDIATE COMPLEMENT-DEPENDENT CYTOTOXICITY OF HUMAN MYELOGENOUS LEUKEMIA BLAST CELLS.

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J Immunol; 128(3):1476-1481 1982

A panel of monoclonal antibodies that bind to leukemic blast cells from patients with acute myelocytic leukemia and chronic myelocytic leukemia in blast crisis was studied for their ability to mediate complement-dependent lysis of a variety of cell populations from patients with leukemia, normal blood cells, and human leukemia cell lines. Several of these monoclonal antibodies were selectively cytotoxic to myeloid leukemia cells (AML-1-99, AML-1-211, AML-2-30, CML-75, CML-115, and CML-150). Although they were all capable of binding to normal cell populations, none of these hybridomas were cytotoxic to normal cells. Three of these antibodies (AML-1-211, CML-75, and CML-150) were cytotoxic to some leukemia cell samples only after dilution of the hybridoma supernatant, ie, they showed a prozone. Binding of these three antibodies as well as another, AML-1-201, as determined in a radioimmunoassay, also showed a prozone. Other monoclonal antibodies are described (AML-2-23 and AML-2-9) that mediate complement-dependent cytotoxicity to myeloid leukemia cells as well as selected normal cell types (monocytes and lymphocytes, respectively). The potential clinical utility of these monoclonal antibodies is considered in the context of recently encountered problems in the use of monoclonal antibodies to mediate leukemia cell lysis in vivo. (Author abstract) (23 Refs)

31. RELATIONSHIP BETWEEN RECEPTORS FOR MOUSE ERYTHROCYTES AND MEMBRANE IMMUNOGLOBULINS IN NORMAL AND LEUKEMIC HUMAN LYMPHOCYTES.

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Medicina (B Aires); 41(Suppl):165-169 1981

Relationship between receptors for mouse RBC (MRBC) and membrane immunoglobulins (mIg) of peripheral lymphocytes in 10 healthy controls (HC: 50-70 yr old) and in 14 patients (similar distribution of sexes and age with the HC) with chronic lymphatic leukemia of B cell type (CLL-B) was studied. All the patients received therapy with corticosteroids and were divided into Group A (6 of the patients with lymphocytes less than 10,000/mm square) and Group B (8 with lymphocytes between 10,000-60.000/mm square). MRBC rosettes for HC were 8% +-2, for Group A were 33.17% +-23.3, and for Group B were 9.12% +- %.2. MRBC rosettes after incubation of lymphocytes with different antibodies were 6% +-3, 8.17% +-6.80, and 2.75% +-2.3, respectively, for anti Ig total. Values for anti IgM and anti IgG were similar to the values f or anti Ig total, while anti IgD was 3% +-2, 11.17% +-7.6, and 2.75% +-3.90, respectively. Cells with mIg total were 17.5% +-5, 20.83% +-11.90, and 19.12% +-10.6, respectively; specific mIgM was 7.2% +-3.2, 11.83% +-9.4, and 5.37% +-4.8, respectively; specific mIgD was tested only for Group B and was 3.12% +-5, and specific mIgG was 10% +-4.5, 10.5% +-5.2, and 8.88% +-6.46, respectively. Relationships between the different values were considered and some hypotheses advanced. (23 Refs) (In SPA)

32. HIGH AND LOW FC IGG-RECEPTOR EXPRESSION IN HUMAN CHRONIC GRANULOCYTIC LEUKAEMIA CELLS.

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Br J Cancer; 45(2):194-200 1982

Discontinuous density-gradient centrifugation was used to separate chronic granulocytic leukemia (CGL) cells in the chronic phase and blast crisis (BC) into fractions containing granulocytes in individual stages of maturation. The occurrence of the Fc IgG (FcR) and complement-component receptors (CR1 and CR2) in each fraction was estimated. It was established that, with increasing yields of mature granulocytes, the proportion of cells bearing Fc and C3 receptors increased. The most important finding was that the high- and low-receptor categories of CGL cells in chronic phase depended on the percentage of FcR+ cells. In the high-receptor CGL group, in addition to FcR, the proportion of CR1+ and CR2+ cells was also greater than in the low-receptor CGL group. Some differences in clinical course of both immunological CGL groups were observed. (Author abstract) (12 Refs)

33. MACROPHAGE MIGRATION INHIBITION ASSAY AS A MEANS OF DETECTING LYMPHOCYTE SENSITIZATION TO LEUKEMIC MYELOBLASTS IN NEUTROPENIC PATIENTS.

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Isr J Med Sci; 17(12):1119-1121 1981

The migration inhibiting factor (MIF) test was performed on 27 patients with chronic neutropenia using acute myeloblastic leukemia (AML) blasts and normal lymphocytes as antigens. Eight patients reacted positively to AML blasts, and the natural history of their disease differed from that of the remaining neutropenic patients: two of the eight patients developed AML and one showed evidence of preleukemic changes. Recurrent severe infections were common and one patient in this group developed systemic lupus erythematosus. The MIF test toward AML blasts may be regarded as a warning sign of a preleukemic state among neutropenic patients. (Author abstract) (11 Refs)

CHEMOTHERAPY

34. EARLY EVALUATION OF THERAPEUTIC RESPONSE IN ACUTE LYMPHOBLASTIC LEUKEMIA. A STUDY OF CYTOREDUCTION IN BLOOD AND BONE MARROW.

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Nouv Presse Med; 11(7):505-507 1982

Cytoreduction was correlated with the remission achievement and the quality of the remission in 27 adults undergoing induction therapy for acute lymphoblastic leukemia. Fifteen patients received induction therapy consisting of vincristine (VCR: 1.4 g/square meter/wk) and prednisone (PDN: 40 mg/square meter/day) administered for 4 wk. Nine patients also received cytarabine (3 g/square meter) on day 3 of induction treatments. Thirteen patients also received chemotherapy with doxorubicin, cyclophosphamide, cytarabine, or methotrexate. Induction therapy produced 19 complete remissions (CR) and 10 failures. The number of circulating blasts did not differ among the two groups. The mean age of the patients in the two groups was the same, 39 yr. A good correlation was observed between decreased cytoreduction and CR. Of the ten patients with a slight decrease in cytoreduction, only one, treated by VCR-PDN, was in CR. None of the other nine patients, including six who had received complementary chemotherapy had CR. Of the 14 patients with the greatest decrease in cytoreduction, only 1 was not in CR. No relationship could be determined between cytoreduction and duration of CR. A significant drop in the absolute blastic index (BI), best appreciated when the bone marrow cellularity was calculated by biopsy, was found in patients who were in CR at the end of induction therapy. Of patients with only a small drop in BI, only one was in CR. The results indicated that early therapeutic cytoreduction has a bearing on the prognosis and that induction treatment should be reinforced in cases where cytoreduction is insufficient. (5 Refs) (In FRE)

35. RESULTS OF INTENSIVE TREATMENT OF 426 CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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Acta Haematol Pol; 12(3/4):175-184 1981

The treatment of 426 children with acute lymphoblastic leukemia is described. Vincristine [VCR: 1.5 mg/square meter (m2) iv] with or without rubidomycin (RBD: 25 mg/m2 iv) was used for remission induction therapy, and the combination of VCR, methotrexate (12 mg/m2 intrathecally with cranial irradiation, and 20 mg/m2 po), cyclophosphamide (200 mg/m2 po), prednisone (40 mg/m2 po) and 6-mercaptopurine (50 mg/m2 po) for maintenance therapy. The remission induction therapy was completed in 393/426 patients: the complete remission rate was 384/393. One hundred and eighty-one patients developed recurrences during the maintenance therapy, and 141 patients died during the first remission, including 123 who died of recurrence of leukemia. Seventeen patients died during long-term remissions. The change of 5-yr survival was found to be 44.8%. The av length of remission has been 50.1 + 2.7 mo so far. Two hundred and eleven patients, including 85 in first remission and 71 with treatment completed, were alive at the time of reporting. The chance of 5-yr survival in another group of patients who were subjected to less aggressive treatment was only 1.2%, and the av lengths of remissions and survival were also significantly shorter. (22 Refs) (In POL)

36. RESISTANCE TO THERAPY OF ACUTE LEUKEMIA DEVELOPING IN THE COURSE OF POLYCYTHEMIA VERA.

Donovan PB, Landaw SA, Dresch C, Gartenhaus WS, Goldberg JD, Ellis JT, Loeb V, Perry MC, Petit RM, Pisciotta AV, Silver RT, Spurr CL, Weinfield A, Berk PD

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Nouv Rev Fr Hematol; 23(4):187-192 1981

Treatment of 13 patients (6 women, 7 men; aged 54-79 yr) who developed acute leukemia in the course of polycythemia vera with a protocol involving vincristine (VCR) and prednisone (PRED) is reported. Twelve patients had acute myelogenous leukemia (AML) and one had acute undifferentiated leukemia. After diagnosis of acute leukemia, each patient received VCR (1.4 mg/square meter (m2)/wk) and PRED (60 mg/m2 daily) for 1 wk; those who achieved remission received 4 more wk of VCR and PRED. Patients who achieved complete remission received monthly maintenance chemotherapy with cytosine arabinoside (Ara-C) and VCR plus PRED. Those who did not achieve partial remission with VCR plus PRED received Ara-C plus adriamycin (ADR). Maintenance therapy after achieving remission consisted of Ara-C and ADR, five patients died within the first 4 wk and only one patient 54 yr old, achieved a complete remission that lasted 38 wk. Median survival was 32 days from initiation of therapy, with 10 deaths during the first 6 wk. One partial remission was observed, but the patient refused further therapy and died after 33 wk. Eleven of the patients who did not achieve complete remission were greater than 65 yr old and six were greater than 70 yr old. (20 Refs)

37. TREATMENT OF ACUTE LEUKEMIA IN ADULTS. I. RESULTS OF INTENSIVE CHEMOTHERAPY IN 106 PATIENTS WITH ACUTE LEUKEMIA.

Janowska-Wieczorek A, Pawelski S, Apel D, Maj S, Gepner-Wozniewska M
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Acta Haematol Pol; 12(3/4):129-135 1981

One hundred and six adult patients with acute leukemia were subjected to intensive remission induction therapy according to one of four different protocols. Protocol I included hydroxyurea, cytosine-arabinoside (ara-C) and rubidomycin (RBD), Protocol II: vincristine ara-C, cyclophosphamide and prednisone (PR), Protol III: ara-C and RBD, and Protocol IV: ara-C, RBD, 6-mercaptopurine and PR. The patients included 93 patients (47 men and 46 women, 16-76 yr old) with acute nonlymphoblastic leukemia (ANLL), 9 of whom were treated according to Protocol I, and 25, 36 and 23 according to Protocol II, III and IV, respectively, and 13 patients (10 men and 3 women, av age 24 yr) with acute lymphoblastic leukemia (ALL), all of whom were treated according to Protocol II. The complete remission rates were 41% for all 106 patients; 37% for the patients with ANLL and 77% for those with ALL. The partial remission rates were 4% for all 106 patients; partial remission occurred in patients with ANLL only. No improvement was seen in 55% of the 106 patients; in 59% of the patients with ANLL and in 23% of those with ALL. The complete remission rates were 22% for Protocol I, 44% for II, 36% for III and 35% for IV for the patients with ANLL. The survival times were 19 wk for Protocol I, 16 wk for II, 20 wk for III and 21 wk for iv for the ANLL patients and 34 wk for those with ANLL in the absence of remission, and 48 wk for Protocol I, 51 wk for II, 34 wk for III and 28.5 wk for IV for the ANLL patients and 56 wk for the ALL patients in the case of remission. Twenty-one patients with ANLL and 2 with ALL died during the intensive chemotherapy. (7 Refs) (In POL)

38. TREATMENT OF ADULTS WITH ACUTE LEUKEMIA. II. PRELIMINARY ANALYSIS OF THE RESULTS OF TREATMENT ACCORDING TO THE AR AND RAMP PROTOCOLS.

Janowska-Wieczorek A, Pawelski S, Maj S, Apel D, Gepner-Wozniewska M
Klinika Chorob Wewnetrznych, Instytut Hematologii, ul. Chocimska 5, 00-957 Warsaw, Poland
Acta Haematol Pol; 12(3/4):137-145 1981

Thirty adult patients with acute leukemias were randomized into two groups for chemotherapy according to two different protocols. Fourteen patients (11 men and 3 women, median age 31.5 yr), including 8 with acute myeloid leukemia (AML), 4 with acute monoblastic leukemia, and 1 each with acute erythroleukemia and acute promyelocytic leukemia (APML), were treated according to Protocol AR [remission induction with cytosine arabinoside (ara-C) and rubidomycin (RBD) in 7-day courses; maintenance therapy with ara-C, RBD, 6-mercaptopurine (6-MP) and cyclophosphamide]. Sixteen other patients (6 men and 10 women, median age 28 yr), including 10 with AML, 5 with acute undifferentiated leukemia and 1 with APML, were treated according to the RAMP protocol (remission induction therapy with RBD, ara-C, 6-MP and prednisone in 5-day cycles; maintenance therapy with 6-MP and methotrexate). The complete remission rates were 7/14 in the AR group and 6/16 in the RAMP group; the partial remission rates were 0/14 and 2/16, respectively. Seven patients in the AR group and eight in the RAMP group showed no improvement. The overall median survival times were 18.5 wk and 28 wk in the AR and RAMP groups, respectively, compared with 32 wk and 28 wk, respectively, for the patients who achieved remissions. The median length of complete remissions has been as yet 15 wk in the RA group and 16 wk in the RAMP group. The incidence of toxic side effects was significantly higher in the RA group than in the RAMP group. The mortality rates within the first 3 therapy cycles were 42.8% in the RA group and 6.2% in the RAMP group. (14 Refs) (In POL)

39. TREATMENT OF ADULTS WITH ACUTE LEUKEMIAS. IV. RESULTS OF TREATMENT OF 375 PATIENTS IN 9 HEMATOLOGICAL CENTERS.

Janowska-Wieczorek A, Gepner-Wozniewska M, Apel D, Bielawiec M, Bodzenta A, Brandowska M, Dabrowski S, Gamski M, Hellman A, Holowiecki J, Japa J, Jarczak D, Kiersnowska-Rogowska B, Kloczko J, Kotlarek-Haus S, Kowalewski J, Kykowski E, Lukjan H, Maj S, Matera M, Mazurowa A, Mysliwiec M, Pawelski S, Robak T, Sowinska J, Urasinski I, Wysocki K
Klinika Chorob Wewnetrznych, Institut Hematologii, ul. Chocinska 5, 00-957 Warsaw, Poland
Acta Haematol Pol; 12(3/4):155-159 1981

The therapeutic results obtained in 375 adult patients (206 men and 169 women, av age 32-43.3 yr) with acute nonlymphoblastic leukemias, treated according to four chemotherapy protocols in 9 hematological centers in Poland, are reported. The complete remission rate was 34.4%, the partial remission rate 22.4%. No improvement was seen in 43.2% of the patients. The duration of complete remissions, evaluated in 93 patients, was 8.8 mo (5.7-11.1 mo for the different therapy protocols). The median survival time was 8.6 mo for 259 evaluated patients; 13.5 mo for the patients who achieved remissions and 3.7 mo for those who did not. Two hundred and ninety-seven of the 375 patients died by the time of reporting. The causes of death included infections in 89 cases, hemorrhagic diathesis in 71, hemorrhagic diathesis and infection in 85, other causes in 32, and the cause of death was unknown in 20 cases. (5 Refs) (In POL)

40. TREATMENT OF ADULTS WITH ACUTE LEUKEMIAS. V. EFFECT OF INTRATHECAL CYTOSTATIC TREATMENT ON LEUKEMIC CHANGES IN THE CENTRAL NERVOUS SYSTEM.

Swencz-Szczepanik K, Pawelski S, Maj S, Krolikiewicz H, Kaczynska D, Koszyk E, Apel D
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Acta Haematol Pol; 12(3/4):161-169 1981

The intrathecal chemotherapy of 82 adult patients (46 men and 36 women, 16-65 yr old) with acute leukemias is described. Forty-eight patients without neurological changes were subjected to prophylactic intrathecal treatment according to one of three methods: 37/48 patients were treated with Method I: methotrexate (MTX: 15 mg) and prednisone (PR: 25 mg); Method II: 7 patients, with cytosine arabinoside (ara-C: 50 mg), and Method III: 4 patients, with MTX (15 mg), ara-C (15 mg) and PR (25 mg). Eight of these 48 patients later developed CNS leukemia despite preventive treatment. The other 34 patients with neurologic al signs of CNS involvement were treated with therapeutic intent along with the 8 patients who developed CNS leukemia after preventive treatment. Method I was applied in 34 patients, Method II in 2, and Method III in 6. Complete neurological remission was achieve by method I in 19 patients, partial remission in 3, complete remission after modification of the therapy in 4, and 4 patients died during the

treatment. Complete remission was achieved in 1/2 patients by Method II and in 5/6 by Method III, while 1 patient each in these two groups died during treatment. (42 Refs) (In POL)

41. A PILOT STUDY OF HIGH-DOSE 1-BETA-D-ARABINOFURANOSYLCYTOSINE FOR ACUTE LEUKEMIA AND REFRACTORY LYMPHOMA: CLINICAL RESPONSE AND PHARMACOLOGY.

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Cancer Res; 42(4):1587-1594 1982

The chemical 1-beta-D-arabinofuranosylcytosine (ara-C), 2 or 3 g/sq m, was administered as a 1-hr iv infusion every 12 hr for 10 or 12 doses to patients with acute leukemia and refractory lymphoma. Four of seven patients with relapsed or refractory acute myelocytic leukemia and two of four patients with previously untreated acute myelocytic leukemia achieved complete remission. Of five treatment failures, two patients had leukemia which was clearly resistant to high-dose ara-C, and three patients died of infections or hemorrhagic complications during periods of pancytopenia. Three patients with acute myelocytic leukemia in remission received high-dose ara-C as consolidation therapy following previous courses of intensive, multiagent consolidation chemotherapy. Two of these three patients had prolonged thrombocytopenia following high-dose ara-C. Five patients with refractory acute lymphocytic leukemia were treated. Three patients achieved partial remission, and two patients had drug-resistant disease. Complete or partial disappearance of measurable disease parameters was seen in three of three patients with refractory lymphoma. Response was seen in five of five patients with meningeal leukemia, including complete response in one patient with extensive meningeal infiltration. Toxicity of this regimen was generally moderate and limited to pancytopenia and mild nausea. Patients who had received prior multiagent consolidation chemotherapy appeared to be at greater risk for hematopoietic toxicity. Patients who had received prior cranial irradiation or intrathecal chemotherapy appeared to be at greater risk for neurological toxicity. Plasma levels of ara-C immediately after completion of the infusion were 17.96 +-8.02 (SD) and 35.0 +-2.8 ug/ml for doses of 2 and 3 g/sq m, respectively. From 160 to 720 min following completion of the infusion, the plasma levels of drug were comparable to steady-state levels achieved with a continuous infusion of ara-C at 100 mg/sq m over 24 hr. A high degree of penetration into the central nervous system was demonstrated. High-dose ara-C has substantial activity against leukemic and lymphomatous cell populations, including cell populations resistant to conventional doses of the drug, and is an effective treatment modality for patients with these diseases. The high degree of penetration into the central nervous system suggests that this drug regimen may be useful as consolidation therapy for patients at high risk for central nervous system disease. (Author abstract) (23 Refs)

42. MODULATION OF 9-BETA-D-ARABINOFURANOSYLADENINE 5'-TRIPHOSPHATE AND DEOXYADENOSINE TRIPHOSPHATE IN LEUKEMIC CELLS BY 2'-DEOXYCOFORMYCIN DURING THERAPY WITH 9-ARABINOFURANOSYLADENINE.

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Cancer Res; 42(5):2092-2096 1982

The effect of the adenosine deaminase inhibitor 2'-deoxycoformycin, on cellular nucleotides during therapy with continuous infusion of 9-beta-D-arabinofuranosyladenine (ara-A) has been investigated. In three courses of treatment using increasing doses, the active 5'-triphosphate of ara-A, 9-beta-arabinofuranosyladenine 5'-triphosphate (ara-ATP), accumulated in leukemic cells and erythrocytes from a patient treated for acute lymphocytic leukemia in proportion to the dose of ara-A. The cellular ara-ATP concentration increased more than five-fold after the injection of a single, nontoxic, but pharmacologically active doses of 2'-deoxycoformycin 24 hr after initiation of ara-A infusion. However, this response was associated with a concomitant increase in the cellular deoxyadenosine triphosphate concentrations to levels equal to or greater than those of ara-ATP throughout the three treatment courses studied. Consistent with previous results using cell-free systems, it was demonstrated that a competitive relationship exists between deoxyadenosine triphosphate and ara-ATP for the inhibition of DNA synthesis in cultured human lymphoblastoid cells and that the ratio of the cellular concentrations of these nucleotides could predict the extent of inhibition of DNA synthesis. Application of this rationale to the nucleotides in the leukemic cells of the patient suggested that administration of 2'-deoxycoformycin may create a cellular biochemical milieu that could be antagonistic to the inhibition of DNA synthesis by ara-ATP. (Author abstract) (32 Refs)

43. PHASE II STUDY OF 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE (NSC 249992) IN CHILDREN WITH ACUTE LEUKEMIA AND LYMPHOMA.

Tan CT, Hancock C, Steinherz PG, Steinherz LJ, Sorell M, Chan KW, Mondora A, Miller DR

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Cancer Res; 42(4):1579-1581 1982

Phase I clinical studies of 4'-(9-acridinylamino)methanesulfon-m- anisidide (AMSA) using several dose schedules have shown acceptable toxicity and antitumor responses in acute leukemia and several carcinomas. Thirty-eight children with acute leukemia and non-Hodgkin's lymphoma were treated with AMSA in a total dose of 140 to 600 mg/sq m given as a daily iv infusion in 2 to 5 days. Maximal tolerated dose was 600 mg/sq m given in 5 days. Complete and partial remissions were seen in 4 of 18 patients with acute lymphocytic leukemia, 0 of 8 patients with acute nonlymphocytic leukemia, and 1 of 5 patients with non-Hodgkin's lymphoma. Marrow apiasia and remissions were also seen with lower doses. The major toxic effects were mucositis, fever, and sepsis which were dose related. Mild nausea and vomiting, transient elevation of serum glutamic oxaloacetic-acid-transaminase, and bilirubin were noted. All of these patients had had prior anthracycline therapy. Abnormal echocardiograms were seen in 14 of 23 patients who had echocardiograms done before and after AMSA. Seven developed congestive heart

failure in association with sepsis in five and with epicardial disease in one. We conclude that AMSA possesses significant activity in childhood leukemia and lymphoma and that studies of AMSA in combination with other effective agents should be done. (Author abstract) (25 Refs)

44. ACLACINOMYCIN A IN ACUTE LEUKEMIAS AND LEUKEMIC NON-HODGKIN LYMPHOMAS.

Mathe G, De Jager R, Hulhoven R, Delgado M, Machover D, Ribaud P, De Vassal F, Gil-Delgado M, Misset JL, Gouveia J, Jasmin C, Hayat M, Gastiaburu J, Schwarzenberg L
Service des maladies sanguines et tumorales, ICIG (INSERM U-50, CNRS L.A.), Centre Claude Bernard, Hopital Paul Brousse, 14-16, av. Paul Vaillant-Couturier, F 94804, Villejuif Cedex, France
Nouv Presse Med; 11(1):25-28 1982

Aclacinomycin A (ACM), a new anthracycline derivative, was administered intravenously to 50 patients in doses of 10-30 mg/m2/day for periods of 6 to 30 days. Among the 45 patients who could be assessed, 17 were suffering from acute myeloid leukemia, 19 from acute lymphoid leukemia and 9 from non-Hodgkin lymphoma. The results confirmed those first published by the authors in 1978 and led them to propose new measures aimed at reducing the toxicity of ACM. Depending on the dosage, complete or partial (more than 50%) remissions were obtained in patients with acute myeloid leukemia. In the 19 patients with acute lymphoid leukemia, complete remission was observed in 2 and partial remission in 2. Among the nine patients with non-Hodgkin lymphoma, there were three complete and one partial remission. ACM did not produce alopecia and, as predicted by the authors' experimental study on hamsters, did not have major cardiac toxicity. The gastrointestinal toxicity, which had forced a reduction of the total dose in the first trial, proved moderate, even with normal dosage. (Author abstract) (20 Refs) (In FRE)

45. SERUM PROFILES OF METHOTREXATE AFTER ITS ADMINISTRATION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA.

Pinkerton CR, Welshman SG, Bridges JM
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Br J Cancer; 45(2):300-303 1982

Serum profiles of methotrexate (MTX) were studied in six children with acute lymphoblastic leukemia given MTX by three different routes: po, im, and iv. MTX (15 mg/square meter) was given po with water after an overnight fast and blood samples were taken from an indwelling venous catheter at 0, 20, 40, 60 min and 1.5, 2, 3, and 4 hr later. Usually within 1 mo, the same dose was given im into the buttock. MTX was given as an iv bolus, diluted to 5 ml with normal saline and injected over 30 sec; blood samples were taken at 0, 10, 20, 40, 60 min and 2, 3, and 4 hr later. Serum was analyzed with the enzyme-linked immunoassay method. Serum profiles were compared with respect to peak MTX concentration, its timing, and drug levels up to 4 hr. In all cases, the po route produced lower peak concentrations than the im route and levels were generally lower throughout the study period. MTX was more rapidly absorbed from the im site and peak concentrations were achieved earlier. While initial concentrations were higher at 10 and 20 min with the iv route, no significant difference between po and iv routes were noted after 2 hr. Generally, the im route produced more sustained concentrations with higher levels at 3 and 4 hr than the other two routes. The rapid decline in concentrations with the iv dose produced lower levels beyond 2 hr than with the im route. Clinical applications of the findings are discussed. (14 Refs)

46. ENZYMATIC STUDIES ON POSSIBLE IMPROVEMENT OF CYTOSINE ARABINOSIDE TREATMENT.

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Scand J Clin Lab Invest; 41(1):29-34 1981

Cell-free extracts of leukocytes, lymphocytes, and granulocytes from 8 patients (11 men, 5 women; 27-62 yr old) with chronic myeloid leukemia (CML) were compared with those from normal cells. Deoxycytidine kinase and cytidine deaminase activities on the natural metabolite deoxycytidine (CdR) and cytosine arabinoside (AraC) revealed that CML-derived leukocyte kinase activity is about 2x as high on AraC as on CdR; no such difference was found for kinase from normal subjects. Deaminase activity was higher in both CML and normal preparations on AraC substrate. No correlation was observed between proliferating neutrophils and nonproliferating neutrophils and the enzyme activities. The cytostatic effect of AraC therapy might be increased in neoplastic CML cells without increasing toxicity to normal cells, by increasing the dose of AraC coadministered with CdR. Normal cells would be protected more than leukemic cells and normal hemopoietic components would be spared. (22 Refs)

RADIOTHERAPY

47. INTRATHECAL RADIOGOLD APPLICATION FOR MENINGOSIS 'PROPHYLAXIS' IN CHILDREN WITH LEUKEMIA AND NON-HODGKIN'S LYMPHOMAS.

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Radiobiol Radiother (Berl); 22(5):659-669 1981

Experience with application of 198Au-radiocolloid gold (RG) for meningosis 'prophylaxis' (MP) in children with leukemia and non-Hodgkin's lymphoma (NHL) is reported. Between 1976 and 1980, 122 children were treated with RG; 108 for MP and 14 for diagnosed meningosis. Four treatments had to be repeated because of insufficient RG distribution, 75 children had new diseases of acute lymphoblastic leukemia (ALL), 5 had NHL, and 6 children had acute myeloid leukemia (AML). Intrathecal RG application with diagnosis and indications, insufficient RG distribution in the cerebral subarachnoid space in children with ALL, MP results in children with leukemias and NHL, and MP results in children with ALL 2-5 yr after treatment start are presented. Among children with NHL, one simultaneous CNS and retrobulbar recurrence occurred. In 3 children with AML, ALL occurred after 5 yr remission, and in 15 with ALL following a hematological recurrence, no CNS recurrences were observed. Twenty-five children (48%) with ALL after RG application are still in complete remission. The results are similar to those obtained with telecobalt irradiation of the scull in combination with intrathecal methotrexate injections but without their side-effects. (In GER)

48. INTRATHECAL RADIOGOLD APPLICATION FOR MENINGOSIS 'PROPHYLAXIS' IN CHILDREN WITH LEUKEMIA AND NON-HODGKIN'S LYMPHOMAS. II. RESULTS AND PROBLEMS FROM THE NUCLEAR MEDICAL POINT OF VIEW.

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Naklearmedizinische Klinik, Stadisches Klinikum Berlin-Buch, Wiltbergstr. 50, DDR-1151 Berlin-Buch, E. Germany
Radiobiol Radiother (Berl); 22(5):670-678 1981

Between 1976 and 1980, 122 children with acute leukemia (AL) and non-Hodgkin's lymphoma (NHL) received intrathecal 198Au-colloid gold (CG) injection and the effects were studied; 108 children were treated for meningosis prophylaxis (MP) and 14 for already diagnosed meningosis. Fifty-seven children were evaluated semiquantitatively (29 girls, 28 boys, 1-14 yr old) for distribution besides the scintigraphic control. Dosese were applied according to the age of patients: 1.5 mCi to 3 patients (1-2 yr old), 2.0 mCi to 1 patient (2 yr old), 2.5 mCi to 1 patient (3 yr old), 3.0 mCi to 41 patients (3-12 yr old), 3.5 mCi to 8 patients (10-13 yr old), and 4.0 mCi to 3 patients (13-14 yr old). Normal CG dis tribution in cerebral and spinal liquor and liver, and CG distribution in cerebral liquor in children with AL and NHL are presented. Fifteen of 57 children did not receive a sufficient dose to the subarachnoid space. Dosimetric problems arise in the irregularities of distribution in the arachnoid space, and computed tomography should be applied for diagnosis. Results of MP with CG can be compared with those obtained for telecobalt therapy with respect to the recurrences. Comparison of both methods is limited because they are based on a different radiobiological effect. (55 Refs) (In GER)

OTHER THERAPEUTIC MODALITIES

49. GLUCOCORTICOID RECEPTORS IN LEUKEMIC CELLS OF CHILDREN WITH ACUTE LEUKEMIA.

Ido M
Dept. Pediatrics, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 31(1):109-125 1981

Levels of glucocorticoid receptors (GCR) in leukemic cells in children with acute leukemia were measured. Blood samples were obtained from 80 patients (41 males and 39 females, 2 mo-22 yr old). Cases included 65 of acute lymphoblastic leukemia (ALL) and 15 of acute myeloblastic leukemia (AML). Binding of [3H]dexamethasone (DMS) was measured with whole cells and with cytosol fractions. Nuclear binding accounted for 60%, cytosol binding for 40%, of total binding. Nuclear binding was proportional to cytosol binding and did not become saturated at DMS levels sufficient to saturate cytosol binding. With DMS levels sufficient to saturate GCR, equilibrium was approached after 90 min. GCR levels, in sites/cell, were 2,827-90,300 (mean 30,039) for patients with ALL and 2,348-40,936 (mean 14,207) for patients with AML. Normal lymphocytes had 1,926-11,438 (mean 6,620) sites/cell. Among patients with ALL GCR levels for 13 patients showing good response to glucocorticoid therapy were 15,050-90,300 (mean 45,451, median 32,508); for 7 patients relapsing within 1 yr 7,525-58,996 (mean 28,233, median 24,682); for 14 poor responders 2,227-22,876 (mean 7,765, median 4,816). Differences between good responders and poor responder were significant; differences between good responders and early relapsers were not significant. GRC levels can apparently be used to predict, to some extent, response to glucocorticoid therapy in patients with ALL, but not to predict duration of remission. (30 Refs)

50. GLUCOCORTICOID RECEPTORS AND LEUKEMIA.

Homo F, Duval D, Marie JP, Zittoun R, Harousseau JL
INSERM U7, Hopital Necker, 161, rue de Sevres, F 75015 Paris, France
Ann Endocrinol (Paris); 42(4/5):315-320 1981

Determination of the number of glucocorticoid (GCC) receptors in peripheral cells and the sensitivity of the cells to hormones in vitro and in vivo is described for 27 patients with acute lymphoblastic leukemia. The number of GCC receptors varied from 2,600 to 19,200 sites/cell and showed great variation among the patients. The mean value of 9,000 sites/cell was 2x that of human circulating lymphocytes. The number of receptors has been studied in relation to the metabolic effects of GCC. The relationship among DNA and RNA synthesis, application of GCC, and the number of GCC receptors has been difficult to determine possibly due to the heterogeneity of the populations studied. A relationship has been found between levels of spontaneous incorporation of tritiated uridine and thymidine and the metabolic effects of the steroid. Differences in GCC receptors between circulating WBC and bone marrow cells suggest that examination of circulating cells does not accurately reflect the behavior of the real target cell of GCC therapy. (32 Refs) (In FRE)

51. GLUCOCORTICOID RECEPTOR STUDIES IN HUMAN LEUKEMIA.

Marchetti P, Natoli V, Raneletti FO, Mandelli F, De Rossi G, Iacobelli S
Lab. Molecular Endocrinology, S. Cuore Catholic Univ., 00100 Rome, Italy
J Steroid Biochem; 15:261-268 1981

Glucocorticoid receptors (GR) and glutamine synthetase (GS) activity were measured in leukocytes from peripheral blood of patients with acute lymphoblastic leukemia (ALL). Problems in GR determination, results for GR and response to glucocorticoid treatment and chemotherapy, and presence and inducibility of GS in ALL cells, are discussed. GR density in leukemic lymphoblasts in ALL correlates positively with the short-term response in glucocorticoid treatment and with the inducibility of complete remission, independent of other prognostic factors. (54 Refs)

MULTIMODAL THERAPY

52. TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA: INFLUENCE OF THREE INDUCTION REGIMENS AND MAINTENANCE WITH CHEMOTHERAPY OF BCG IMMUNOTHERAPY.

Omura GA, Vogler R, Lefante J, Silberman H, Knospe W, Gordon D, Jarrell R
Univ. Alabama Birmingham, 638 Zeigler Building, University Station, Birmingham, AL, 35294
Cancer; 49(8):1530-1536 1982

The effect of a synchronizing-recruiting drug schedule vs myelotoxic therapy on remission rate and of Bacillus Calmette-Guerin on remission duration and survival of adults with acute myelogenous leukemia were studied in a prospective cooperative trial. After randomized remission induction with Arabinosyl Cytosine + vincristine + methotrexate + leucovorin (AVML), thioguanine + Ara-C + Daunorubicin (TAD), or Daunobrubicin + Ara-C (DA), complete remissions (CR) were

consolidated with TAD or AVML. CRs were maintained with BCG vaccination (Tice strain) by the tine technique, or BCNU plus Ara-C (B/A), or no further therapy (NFT). Of 209 evaluable TAD patients, 105 (50%) achieved CR; of 187 DA, 97 (52%) achieved CR. AVML yielded only 15 CR among 59 patients (25%). The time to remission was significantly shorter with DA compared with TAD. Ninety-seven patients were randomized to maintenance therapy (35 B/A, 30 BCG, 32 NFT). There were no differences in remission duration (7, 8, 6 mo) or survival (16, 22, 16 mo, respectively). Manipulation of the cell cycle, as employed in this study, was not helpful. There may be a marginal effect of BCG, but our data fail to show a statistically significant benefit. (Author abstract) (22 Refs)

53. TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA. RESULTS IN 1,192 PATIENTS.

Sackmann Muriel F, Bcstelo P, Pavlosky S, Eppinger-Helft M, Svarch E, Brnier JL, Garay R, Vergara B, Birman V, Peralver J, Kvicala R, Divito J, Failsce R, Dibar E
Hospital de Ninos, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):5-14 1981

Between 1967-1978 1,005 children (less than 15 yr old) and 187 adults underwent treatment for acute lymphoblastic leukemia (ALL). All the patients were evaluated in April of 1981. None of the patients received any previous treatment. Four different protocols were used, all of them included vincristine (VCR), prednisone (PRED), daunorubicin (DNR), and methotrexate (MTX). Complete remission was achieved in 872/1,005 of the children and in 113/187 of the adults. Induction therapy with DNR, VCR, and PRED was more effective than only VCR and PRED. Prevention of CNS involvement was accomplished effectively with cranio-cervical radiotherapy (2,400 rad) and 5 doses of the intrathecal administration of MTX. Additional administration of MTX and dexamethasone did not improve the results. Intensification phase with l-asparaginase or arabynosyl cytosine (AC) and cyclophosphamide (CY) did not improve the results of the not treated control group. In maintainance phase best results were obtained with daily doses of 6-mercaptopurine and MTX twice weekly. Reinforcement with AC and CY alternating with VCR and PRED prolonged complete remission in children with initial WBC less than 50,000/ml. Adjuvant immunotherapy with levamisole prolonged the complete remission and increased survival. (25 Refs) (In SPA)

SUPPORTIVE CARE

54. IMMUNOHISTOLOGY OF GRAFT-VERSUS-HOST DISEASE MEDIATED SKIN LESIONS AND ITS CORRELATION TO A LARGE GRANULAR LYMPHOCYTE SURFACE PHENOTYPE AND FUNCTION.

Muller C, Schuch K, Pawelec G, Wilms K, Wernet P
Abteilung II, Medizinische Universitatsklinik Tubingen, Otfried-Muller-Strasse, D-7400 Tubingen, W. Germany
Blut; 44(2):89-94 1982

Skin biopsy specimens from five leukemia patients with graft-versus host disease (GVHD) were compared to specimens from normal individuals and from leukemia patients prior to treatment. Expression of cell-surface antigens was measured by immunofluorescence tests using selected monoclonal antibodies. Normal skin from two normal individuals and two leukemic patients showed human lymphocyte antigen (HLA)-ABC on all epidermal keratinocytes from the basal cell layer to the stratum granulosum and in the der mis on fibroblasts, mononuclear cells, blood vessel endothelium, and sweat gland epithelium. No HLA-ABC was found in the outer horny layer of epidermis. HLA-D/DR were found in the dermis on rare irregular mononuclear cells, a subpopulation of fibroblasts, and blood vessel epithelium. In the epidermis HLA-D/DR were found only on a small population of dendritic cells. Ia+, HLA-D/DR+ cells were concentrated in suprabasal epidermal layers. Skin from patients with acute GVHD showed normal distribution of HLA-ABC. Cells bearing HLA-D were concentrated in the upper dermis and at some points appeared to invade and destroy the basal cell layer of the epidermis. 1+, Ia+ Langerhans cells were reduced within the epidermis. Chronic GVHD was marked by hyperkeratosis in one case and general epidermal atrophy in one case. HLA-D+ mononuclear dermal cells and Langerhans cells were reduced in one chronic patient. Onset of chronic and acute GVHD was marked by infiltration of the dermis by HLA-D+ cells resembling mature T cells, suggesting that skin lesions result from cell-mediated cytotoxicity effected by a population of T cells. Skin biopsy may be useful as a diagnostic aid in GVHD. (9 Refs)

55. USE OF ANTI-T-CELL MONOCLONAL ANTIBODY OKT3 TO PREVENT ACUTE GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC BONE-MARROW TRANSPLANTATION FOR ACUTE LEUKAEMIA.

Prentice HG, Janossy G, Skeggs D, Blacklock HA, Bradstock KF, Goldstein G, Hoffbrand AV
Academic Dept. Haematology, Royal Free Hosp. Sch. Medicine, London, England
Lancet; 1(8274):700-703 1982

Seventeen patients who received allogeneic bone-marrow transplants from matched or slightly mismatched (in 4 patients) siblings were observed for at least 60 days or until acute graft-vs-host disease (GvHD) developed. All donor marrows after preliminary manipulation were incubated with 1 mg of the murine monoclonal antibody OKT3 before infusion in an attempt to deplete them of immunocompetent T lymphocytes (opsonization). In 3 of the 17 patients acute GvHD of Grade II or greater developed. Two of these patients died, but they had disseminated cytomegalovirus infection as well as GvHD. Eleven patients showed no evidence of acute GvHD, and 4 had transient limited skin rashes (Grade I GvHD). Opsonization of T Lymphocytes has reduced the incidence of severe acute GvHD in this unit from 79% in an earlier group of 14 patients to 18% when added to prophylactic methotrexate. (Author abstract) (33 Refs)

56. FACTORS ASSOCIATED WITH INTERSTITIAL PNEUMONITIS AFTER BONE-MARROW TRANSPLANTATION FOR ACUTE LEUKEMIA.

Bortin MM, Kay HE, Gale RP, Rimm AA
Mount Sinai Medical Center, P.O. Box 342, Milwaukee, WI, 53201
Lancet; 1(8269):437-439 1982

Data from 176 patients with acute leukemia given allogeneic marrow transplants between January 1, 1977, and December 31, 1980, and reported to the International Bone Marrow Transplant Regi stry were analyzed retrospectively for prognostic factors associated with the development of interstitial pneumonitis (IPn). The overall incidence of IPn was 20% (36/176), and the disease was fatal in 21 of the 36 cases (58%). Three of more than 30 prognostic factors studied seemed to be

associated with a low risk of IPn-pretransplant total body irradiation at a dose-rate less than or equal to 5.7 cGy/min, when compared with higher rates (p less than 0.001); post-transplant immunosuppression with cyclosporin A, when compared to methotrexate (p less than 0.0003); and transplantation of cells from female donors into female recipients, when compared with female donors and male recipients (p less than 0.0005). The low dose-rate of total body irradiation and the use of cyclosporin-A were considered as independent variables, but were confounded to the extent that it was not possible to determine if one or both factors were associated with a decreased incidence of IPn. (Author abstract) (12 Refs)

57. A PROSPECTIVE STUDY OF PLATELET-TRANSFUSION THERAPY ADMINISTERED TO PATIENTS WITH ACUTE LEUKEMIA.

Kutti J, Zaroulis CG, Dinsmore RE, Reich L, Clarkson BD, Good RA
Sloan-Kettering Inst. Cancer Res. and Dept. Medicine, Eastern Hosp., Gotenborg, Sweden
Transfusion; 22(1):44-47 1982

Nineteen recently diagnosed patients with acute leukemias received prophylactic platelet transfusions when thrombocytopenic. Platelet concentrates were always transfused within 8 hours of collection. The result of each transfusion was carefully monitored for the posttransfusion platelet increment. One patient died 4 days after admission to the present study. Seven patients died 1 to 14 months after the institution of antileukemic chemotherapy. Four patients received marrow transplants 1 to 2 months after starting chemotherapy and, therefore, were no longer evaluated in this study. One patient was lost to follow-up after 7 months of observation. The remaining six patients are alive and have been followed for 9 to 18 months. During the period of observation, none of the patients developed any evidence of refractoriness to platelet transfusion therapy. Although this series does not permit any firm conclusions to be made, it appears that the magnitude of the problem of alloimmunization to platelet transfusion therapy may be overemphasized. (Author abstract) (11 Refs)

58. ANALYSIS OF TWO TYPES OF GRANULOCYTE TRANSFUSIONS IN PATIENTS WITH ACUTE LEUKEMIA AND SEPTICEMIA.

Morse EE, Snyder E, Blumberg N, Katz AJ
Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Ann Clin Lab Sci; 12(2):106-110 1982

Two types of granulocyte transfusions were administered to patients with acute leukemia and septicemia: 45 patients (26 females, 19 males) received granulocytes prepared by centrifugation (CG) and 36 (14 females, 22 males) received granulocytes prepared by filtration (FG). No significant difference in distribution of organisms was observed between CG and FG. Patients receiving FG had a few more Escherichia coli while those receiving FG CG had a few more Klebsiella. Three patients receiving FG had Candida albicans septicemia. Recovery from infection was significantly better in patients receiving CG (32 recovered/13 failed) than those given FG (16 recovered/20 failed). Seventeen of 29 patients (59%) with gram negative septicemia receiving CG recovered compared with 11/26 receiving FG. Of those with gram positive septicemia, 15/16 given CG and 4/7 given FG recovered. Further development of centrifugation or sedimentation techniques for obtaining granulocytes for transfusion is warranted. (25 Refs)

59. FETAL LIVER TRANSPLANTATION IN 2 PATIENTS WITH ACUTE LEUKAEMIA AFTER TOTAL BODY IRRADIATION.

Lucarelli G, Izzi T, Porcellini A, Delfini C, Galimberti M, Moretti L, Polchi P, Agostinelli F, Andreani M, Manna M, Dallapiccola B
Divisione Ematologica di Trebbiantico, Ospedale di Pesaro, 61100 Pesaro, Italy
Scand J Haematol; 28(1):65-71 1982

Two patients with acute leukemia in relapse were transplanted with fetal liver cells following a conditioning regimen of cyclophosphamide (120 mg/kg) and total body irradiation (1,000 r). Each patient achieved a remission with hematopoietic recovery that was rapid in one case and delayed in the other. In one case there was evidence of chimerism as demonstrated by the presence of the XYY karyotype of the donor fetus in 20% of marrow metaphases, by the presence of double Y bodies in the peripheral blood, by the appearance of new HLA-antigens, and by red cell isoenzyme phenotypes of donor origin. In the second case there was prompt hematopoietic recovery and the appearance of red cell isoenzyme phenotypes of donor origin. Survival was 153 and 30 day, respectively, and both patients died of interstitial pneumonia without evidence of graft versus host disease. (Author abstract) (28 Refs)

60. PERIODONTAL INFECTION IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKEMIA.

Overholser CD, Peterson DE, Williams LT, Schimpff SC
(c/o Peterson) Dept. Oral Diagnosis, Coll. Dental Surgery, Dental Sch., Univ. Maryland, 666 W. Baltimore St., Baltimore, MD, 21201
Arch Intern Med; 142(3):551-554 1982

From the initiation of chemotherapy until attainment of complete remission, 22 newly diagnosed, hospitalized patients with acute nonlymphocytic leukemia were studied for the prevalence of periodontal disease at admission and for acute exacerbations during myelosuppressive chemotherapy. Consistent with a normal population, all patients had asymptomatic periodontal disease at admission. In these 22 patients, 47 acute infections developed, including 13 of periodontal origin. All but three acute pe riodontal infections occurred during pronounced granulocytopenia (less than 100 granulocytes per microliter). Although signs and symptoms of inflammation were minimal, all 13 episodes were associated with pain and fever. Asymptomatic periodontal disease is readily overlooked but can be easily diagnosed by thorough clinical and roentgenographic examination. Its occurrence in patients with acute leukemia and its acute exacerbation during granulocytopenia indicate that this oral infection is associated with considerable morbidity during the treatment of acute nonlymphocytic leukemia. (Author abstract) (17 Refs)

61. ETIOLOGY OF INFECTIONS IN NEUTROPENIC PATIENTS WITH ACUTE LEUKEMIA: RESULTS OF TWO ANTIBIOTIC COMBINATIONS.

Scaglione C, Lopez H, Fernandez A, Marcenac F, Garay G, Dupont J, Pavlovsky S
Departamento de Oncohematologia, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):29-34 1981

Etiology and location of febrile episodes (FE) and efficacy of the antibiotics cephapirin plus amikacin (CA) and cephalothin plus tobramycin (CT) were examined in 86 neutropenic patients (49 children, 37 adults), 49 with acute lymphoblastic leukemia and 37 with acute myeloblastic leukemia. Thirty-seven patients were in the induction phase of therapy, 30 in the

maintainance phase, and 19 in relapse. All antibiotics were administered iv for at least 7 days. FE were caused by bacteria in 18 cases (72% Gram positive, 22% Gram negative, and 6% fungal) and were documented clinically in 30. Organisms isolated in culture included Candida albicans and various Streptococci. FE were located in the respiratory tract (39 patients), skin and soft tissue (9), sepsis (18), or were of unknown origin (17). Of 86 FE, 42 were treated with CA and 76% showed improvement, while 44 FE were treated with the CT and 66% showed improvement. All patients with diffuse interstitial pneumonia and Gram negative bacteria did not respond to therapy with CA and CT. Rapid recovery from neutropenia was related to improvement in FE. Secondary nephrotoxicity was an infrequent complication. (14 Refs)

CASE REPORTS

62. TWO CASES OF GRAFT-VERSUS-HOST DISEASE FOLLOWING TRANSFUSION OF NONIRRADIATED BLOOD PRODUCTS.

Schmitz N., Kayser W, Gassmann W, Huhn A, Kruger G, Sachs V, Loffler H
II. Medizinische Klinik, Universitat Kiel, Metzstrasse 53, D-2300 Kiel, W. Germany
Blut; 44(2):83-88 1982

Graft-versus-host disease (GVHD) in two leukemia patients after transfusion of nonirradiated blood products is reported. A 38-yr-old man was treated for acute myelomonocytic leukemia by polychemotherapy with cyclophosphamide, cytosine arabinoside (Ara-C), and VP16-213 (200 mg of each drug for 3 days). Nonirradiated packed RBC and platelets had previously been transfused because of anemia and th rombocytopenia. The patient became cytopenic and feverish. A maculopapular rash appeared on the head and face 25 days after the first granulocyte transfusion. Jaundice became evident 3 days later. The peripheral granulocyte count rose above 1 x 10(9)/liter and stabilized at that level. Bone marrow aspirates indicated normal hematopoiesis. GVHD was indicated by skin biopsy at day 41. Two wk later extensive desquamation of skin occurred and jaundice began to disappear. The patient was discharged in complete remission of leukemia and free of disease 8 mo after initial diagnosis. A 19-yr-old man was treated for acute myeloblastic leukemia with Ara-C, adriamycin, and thioguanine. Severe pancytopenia and fever developed. A macropapular rash developed over most of the patient's body 8 days after the first transfusion of packed RBC and 3 days after transfusion of platelets. Pancytopenia was indicated on day 17 by bone marrow aspiration; no evidence of leukemic cells was found. The patient died after 30 days; clinical signs indicated diffuse peritonitis and septic shock. Skin biopsy 1 day before death indicated GVHD. Irradiation with at least 1,500 rad of all blood products administered to patients undergoing aggressive cancer therapy is urged. (17 Refs)

63. DESQUAMATIVE INTERSTITIAL PNEUMONITIS ASSOCIATED WITH MONOMYELOCYTIC LEUKEMIA.

Goldstein JD, Godleski JJ, Herman PG
Dept. Pathology, Brigham and Women's Hosp., Boston, MA, 02115
Chest; 81(3):321-325 1982

Cases of two women (51 and 48 yr old) who presented with untreated, subacute, monomyelocytic leukemia (MML) at the onset of pulmonary symptoms of desquamative interstitial pneumonitis (DIP) are described. The first patient had a 3-wk history of classic symptoms of DIP. The WBC count, subsequently interpreted as acute leukemia, was 50,000 with 30% atypical monocytes and 5% blasts. Bone marrow biopsy suggested chronic MML. Treatment with prednisone led to clinical and radiographic resolution of the pulmonary abnormalities beginning within 1 wk. Chemotherapy with cyclophosphamide, vincristine, arabinoside-C, and prednisone led to gradual improvement. Twenty mo after the onset of illness the patient died. The second patient presented with rheumatoid arthritis of approx 8 mo duration. A diagnosis of probable MML was made. The patient's hematologic status remained stable without treatment. Three yr later the arthritic symptoms increased and pulmonary infiltrates were noted; 2 mo later dyspnea developed and the pulmonary infiltrates had become widespread and confluent. The patient died 2 days later. Histology of open lung biopsies in both cases was similar to that of other patients with DIP. Immature WBC were observed in the interstitia and extensive intravascular stasis of leukemic cells was present in the postmortem specimen in the second patient. Pathogenesis of DIP in the patients is discussed. DIP should be considered a possible cause of pulmonary infiltrates in patients with hematological malignancy. (20 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

64. NATURAL ANTIBODIES TO THE STRUCTURAL CORE PROTEIN (P24) OF THE HUMAN T-CELL LEUKEMIA (LYMPHOMA) RETROVIRUS FOUND IN SERA OF LEUKEMIA PATIENTS IN JAPAN.

Kalyanaraman VS, Sarngadharan MG, Nakao Y, Ito Y, Aoki T, Gallo RC
(c/o Gallo) Lab Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(5):1653-1657 1982

We investigated the involvement (in adult T-cell leukemias and lymphomas) of the human T-cell leukemia virus (HTLV) that was previously isolated in one of our laboratories from cultured T cells of some patients in the United States with leukemias and lymphomas involving relatively mature T cells. High titers of antibodies capable of quantitative precipitation of 125I-labeled p24, a well characterized core protein of HTLV, were detected in 12 of 12 patients with untreated adult T-cell leukemia (ATL). (1 negative was a patient on chemotherapy). Ten of the 12 positive samples were from an area where the disease is endemic. Strong precipitating antibodies were also detected in five of seven cases of T-cell malignant lymphoma (TML) which differs from ATL by having fewer leukemic cells in the peripheral blood. High antibody titers were also observed in one of five cases of acute monoblastic leukemia and one of eight cases of chronic myelogenous leukemia in the blast phase of the disease. Low to moderate titers of antibodies were detected in several categories of leukemia (2 cases of blast-phase chronic myelogenous leukemia, 2 cases of acute lymphoblastic leukemia of the null-cell type, and 1 case of acute myelogenous leukemia). Among all categories of leukemias, except ATL and TML, more cases were negative than positive for anti-p24 activity. All of 79 sera from normal Japanese, including 39 collected from the endemic ATL area of southwest Japan, were negative for antibodies to HTLV p24. All the positive reactivities observed were highly specific to HTLV. The only competition observed in the precipitation of

HTLV p24 was with HTLV or with cell lines expressing HTLV and not with various animal retroviruses or a large number of human and subhuman primate cell lines, not known to be producing HTLV. The data strongly indicate an association of HTLV with the increased incidence of ATL in parts of Japan, probably with other forms of leukemias in Japan, and, less commonly, with certain T-cell malignancies in the United States (26 Refs)

65. ADULT T-CELL LYMPHOMA-LEUKAEMIA IN BLACKS FROM THE WEST INDIES.

Catovsky D, Rose M, Goolden AW, White JM, Bourikas G, Brownell AI, Blattner WA, Greaves MF, Galton DA, McCluskey DR, Lampert I, Ireland R, Bridges JM, Gallo RC
Medical Res. Council Leukaemia Unit, Royal Postgraduate Medical Sch., London, England
Lancet; 1(8273):639-642 1982

Six Black patients (5 born in the West Indies and 1 in Guyana), aged 21-55 yr, had adult T-cell lymphoma-leukemia diagnosed in the UK This disorder is rare in Europe and the USA, but is more common in Japan. Five patients had severe hypercalcemia which correlated with disease activity, although osteolytic lesions were found in only one. Other clinical features were lymphadenopathy and a high white blood-cell count (range 27-67 x 10(9)/l) with a predominance of pleomorphic lymphoid cells with pronounced nuclear irregularities prominent at ultrastructural level. The cells in all cases formed rosettes with sheep red blood-cells and lacked terminal transferase. Analysis with OKT monoclonal antibodies in four cases confirmed a mature T-cell phenotype defined as helper/inducer (T4+, T6-, T8-) in three. Combination chemotherapy resulted in short-lived remissions; four patients died and two have survived 3-6 mo. The disease in these patients is indistinguishable on clinical and pathological grounds from adult T-cell leukemia/lymphoma in Japan. Geographical clustering among certain racial groups suggests common etiological factors in the pathogenesis of this disease. The finding of high titer antibody against the structural core protein (p24) of a new human C-type leukemia virus (human T-cell leukemia/lymphoma virus) in all tested cases from this series and data from all but one case from Japan suggest that one such factor may be viral. (Author abstract) (no Refs)

SELECTED PRE-CLINICAL STUDIES

66. EFFECTS OF PARTIALLY THIOLATED POLYCYTIDYLIC ACID AND LIPOSOMES ON IN VITRO COLONY-FORMING CELLS OF LEUKEMIC MICE.

Ho YK, Mayhew E, Preisler HD, Bardos TJ
Dept. Biophysical Sciences, State Univ. New York at Buffalo, Buffalo, NY, 14214
Cancer Res; 42(5):1740-1743 1982

Partially thiolated polycytidylic acid (MPC), an antileukemic agent, when administered to leukemic RF/UN mice inhibited the clonogenicity of bone marrow progenitor cells in a time- and dose-dependent manner. The effect of a single dose of MPC disappeared within 40 hr due to the rapid degradation of this compound in mice. When MPC was encapsulated in liposomes before injection, its activity at 19 hr after inoculation was similar to that of free MPC. The inhibitory effect of this liposome-MPC complex, however, persisted for at least 40 hr, indicating that the MPC was protected from hydrolysis by the nucleases present in blood. Drug-free liposomes increased the number of clonogenic progenitor cells, whereas a mixture of plain liposomes and MPC decreased the number of clonogenic cells to a greater extent than did MPC alone or MPC within liposomes. A possible explantation for these observations is that the liposomes per se altered the cle arance function of the reticuloendothelial system and competed with MPC for uptake by the reticuloendothelial system cells, thereby resulting in increased plasma levels of MPC which in turn resulted in greater killing of the target cells. (Author abstract) (23 Refs)

67. METABOLIC AND ULTRASTRUCTURAL ASPECTS OF THE IN VITRO LYSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS BY GLUCOCORTICOIDS.

Galili U, Leizerowitz R, Moreb J, Gamliel H, Gurfel D, Polliack A
Dept. Hematology, Hadassah Univ. Hosp., Kiryat Hadassah, P. O. B. 12000, IL-91 120 Jerusalem, Israel
Cancer Res; 42(4):1433-1440 1982

Human chronic lymphocytic leukemia (CLL) cells like prothymocytes and immunoactivated T-lymphocytes are readily lysed in vitro by pharmacological concentrations of glucocorticoids such as cortisol, whereas peripheral blood lymphocytes and thymocytes are unaffected by the hormone. In this study, metabolic and ultrastructural aspects of the cortisol-induced killing process of CLL cells are recorded. In vitro lysis was found to be temperature dependent and was detected only after 6 to 8 hr incubation with cortisol by means of the trypan blue exclusion test. However, 30 min of incubation with cortisol at either 37 C or 4 C followed by the removal of the hormone was still sufficient to induce the lytic process. Ultrastructural studies demonstrated sequential changes in the cytoplasm, including swelling of mitochondria and cytoplasmic decompartmentalization, followed by loss of surface microvilli with the appearance of 'holes' in the cell membrane, and subsequent condensation of nuclear chromatin. The large holes in the membrane appearing after 6 hr of incubation with the hormone may be the cause for the penetration of the viable stain into the dead cells, as seen by light microscopy. Addition of metabolic inhibitors including actinomycin D, puromycin, and cycloheximide following administration of cortisol resulted in inhibition of the cell lysis. An excess of an antagonist such as cortexolone was found to inhibit the cortisol-induced cytolysis of the CLL cells. It is suggested that the glucocorticoid-induced lysis of human CLL cells is similar to the phenomenon observed in rat or murine lymphocytes and is mediated by interaction of the steroid molecule with the cytoplasmic receptor. The resulting complex appears to activate specific gene(s) the products of which eventually cause cytolysis. (Author abstract) (30 Refs)

REVIEWS

68. LEUKEMIA: HISTORICAL DEVELOPMENT OF CANCER THERAPY: THE FIRST BATTLE IS WON.

Evans AE
Div. Oncology, Cancer Center, Children's Hosp. Philadelphia, Univ. Pennsylvania, Philadelphia, PA, 19104
Front Radiat Ther Oncol; 16:18-29 1982

The combination chemotherapy protocols which had been developed by 1975 increased the 5-yr disease-free survival (DFS) rate to 50% in children with acute lymphocytic leukemia (ALL). Most relapses occur in the first 2.5 yr. When maintenance therapy is given for 5-6 yr instead of 2.5-3 yr, the

DFS rate is not greatly increased, except in boys who tend to develop testicular involvement. Studies on the natural history of childhood ALL have led to the formulation of a set of prognostic factors: age (the best prognosis is in children 2-10 yr old), sex (the prognosis is better in girls than in boys), initial WBC count, the presence or absence of CNS involvement and/or a lymphoma syndrome (elevated Hb, markedly enlarged liver, spleen, and lymph nodes, and/or a mediastinal mass), IgG levels (depression of IgG is an unfavorable sign), FAB markers on the leukemic blasts, and marrow status on day 14 of therapy. The presence of B- or T-cell markers on the leukemic cells is not in itself a major factor. The unfavorable prognosis of T-cell ALL is primarily related to its association with older age, male sex, a high WBC count, and a mediastinal mass. If these factors are not present, the occurrence of T-cell markers is not an unfavorable factor in itself. The 5-yr DFS rate in children having a good prognosis is now 90%. It may be possible to achieve equally good results in these patients with less intensive therapy. Recent advances in treatment have not given such good results in acute leukemias other than ALL. High-dose chemotherapy and total-body radiation, followed by bone marrow transplants from an HLA-identical sibling, have led to a 2-yr survival rate of 60%, if this treatment is given during the first remission. The late effects of successful treatment are now being investigated. (30 Refs)

* U. S. GOVERNMENT PRINTING OFFICE: 1982—361-847/123

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SEPTEMBER, 1982

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DIAGNOSIS

1. CHEST X-RAY MANIFESTATIONS OF ACUTE LEUKEMIA.

Li G, Wei D
Guangdong Provincial Hosp., Guanghow, People's Republic of China
Chin Med J [Engl]; 94(12):816-820 1981

Chest x-ray films collected from hospital files of 49 acute pediatric leukemia patients (32 males, 17 females: 1-13 yr old) were analyzed. The series included 37 acute lymphatic leukemia (ALL), 10 acute granulocytic leukemia (AGL), and 2 acute monocytic leukemia (AML). Thirty-five patients had positive x-ray findings. The autopsy material of four ALL and one AML were reviewed for lung, lymph node, and pleural changes. In one patient, the chest x-ray taken 9 days prior to death and the pathologic findings were compared. Positive

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roentgenologic findings were observed in 71.4% of the patients. Pulmonary changes (PC) were observed in 27 patients. PC occurred more often alone (70% AGL, 54% ALL) than in association with other changes. Mediastinal and hilar glandular enlargements were observed in 19 patients (16 ALL, 3 AGL). Findings in five autopsies included pulmonary edema in four, bronchopneumonia and pulmonary hemorrhage in three each, leukemic infiltration in two, and atelectasis in one case. Bronchopneumonic or pneumonic consolidation with concomitant respiratory symptoms may indicate infection. (7 Refs)

2. ABDOMINAL MANIFESTATIONS OF PEDIATRIC LEUKEMIAS: SONOGRAPHIC ASSESSMENT.

Gore RM, Shkolnik A
Dept. Radiology, Univ. California Medical Center, San Francisco, CA
Radiology; 143(1):207-210 1982

The abdominal sonograms of 64 leukemic children were reviewed and correlated with clinical, hematological, and, when available, autopsy findings. Sonographic abnormalities including enlargement of the liver, spleen, pancreas, and kidneys, with or without alteration of parenchymal echo architecture, hydronephrosis, lymphadenopathy, and ascites were encountered in 70% of the patients. Ultrasound proved useful in detecting occult visceral leukemia and relapse, monitoring tumor response to chemotherapy, and assessing the complications of chemotherapy. Ultrasound is recommended for the routine evaluation and follow-up of the pediatric leukemic patient. (Author abstract) (20 Refs)

3. DIAGNOSIS OF ACUTE LEUKEMIA IN 70 CASES: THE APPLICATION OF FAB CLASSIFICATION AND ITS PROBLEM.

Tsuchiya T, Kumasaka K, Kawano K, Ohshima T, Kuwashima M
Dept. Clinical Pathology, Nihon Univ. Sch. Medicine, Japan
Rinsho Ketsueki; 22(12):1897-1908 1981

Four hematologists (A,B,C, and D) were asked to diagnoses 70 cases of acute leukemia from specimens and classify them according to the French American British (FAB) system in order to examine reproducibility and agreement of diagnosis. Specimens were stained with Wright-Giemsa staining (Romanowsky stain) or peroxidase staining. The diagnosis initially made by A was used as the diagnostic criteria. In the first trial, the reproducibility shown by A was 90.3%. The agreement displayed by the others was: 80.6% by B, 66% by C, and 43.5% by D. After the first trial, the panelists discussed 24 selected cases. After excluding deteriorated specimens and those belong to dysmyelopoietic syndrome according to the FAB classification, the remaining 46/70 cases were again routed to the four panelists for diagnosis. Agreement was 84.8% between panelists A, B, and C, and 67.4% between all four. Difficulties in obtaining a complete agreement occurred in the identification of L1 and L2, M1 and M2, variability of M1 and M4 cases, and some problems in determining M3, M5, and M6. In the FAB classification, identification is based on the percentage of cell examination, and therefore it is more empirical than theoretical, making the system convenient to use. However, there are cases that do not fit well with the FAB classification. To resolve such cases, it is desirable to examine the surface markers of leukemic cells, antigenicity, enzyme activity, electron micrograph and chromosome analysis, and compare with typical cases. Before an appropriate evaluation can be made, the FAB classification must be popularized in Japan. (17 Refs) (In JPN)

4. ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDHOOD: IMPORTANCE OF SEX AS A PROGNOSTIC FACTOR.

Kuchler H, Buriot D, Maier M, Griscelli C
(c/o Griscelli) Unite d'Immunologie et d'Hematologie, Groupe Hostpitalier Necker-Enfants-Malades, Departement de Pediatrie, 75730 Paris Cedex 15, France
Arch Fr Pediatr; 39(1):17-21 1982

Clinical and biological prognostic criteria were examined in 63 patients (36 males, 27 females; less than 15 yr old) with acute lymphoblastic leukemia (ALL), who had been followed up for 3 or more yr. ALL had been diagnosed in 11 patients less than 2 yr old, in 43 between 2 and 8 yr old, and in 9 patients more than 8 yr old. High WBC counts were observed in 15 patients, and tumors in 31. ALL with high WBC counts were often associated with tumors (12/15 cases); nontumoral forms usually did not have elevated WBC counts (29/32). Increased numbers of WBC were found in 11/36 males and in 4/27 females. Tumors were found in 20/36 males, and 11/27 females. The median number of WBC was 8.4 x 10(9)/ liter for males and 6.2 x 10(9)/liter for females. After 3 yr, 33/63 patients were in first remission. Leukemic relapse was noted in 30 other patients. Hematological (17 patients), meningeal (7), and testicular (4) relapses were observed. Of the 43 patients followed for 5 or more yr, 13 were in first remission while 30 others had relapsed after a mean remission of 24 mo. Of the criteria studied, only sex and elevated WBC levels showed a significant correlation with survival. (38 Refs) (In FRE)

5. LYSOSOMAL GRANULES IN LEUKEMIC MONOCYTES AND THEIR RELATION TO MATURATION STAGES.

Catovsky D, O'Brien M
MRC Pathology, Hammersmith Hosp., Royal Postgraduate Medical Sch., Ducane Road, London W12 OHS, England
Haematol Blood Transfus; 27:167-173 1981

Bone marrow and/or peripheral blood cells from 11 patients with monocytic leukemia were studied with light and transmission electron microscopy (TEM) cytochemical techniques. Two of the patients had monoblastic transformation of chronic granulocytic leukemia. Seven patients had poorly differentiated and four had differentiated leukemia. Cytochemical reactions for myeloperoxidase (MPO), Sudan Black B, acid phosphatase (AP), naphthol-AS acetate esterase, and alpha naphthyl acetate esterase were performed. TEM was used to examine cell morphology and for evaluation and localization of MPO and AP activity. Conventional TEM in two cases revealed typical ribosome-lamella complexes. AP and MPO reactions at the TEM level revealed three types of lysosomal granules: primary granules were the smallest in size, were mainly seen in monoblasts and were characteristically AP positive; secondary granules were seen from the promonocyte stage onwards, were of medium size, were MPO positive with some AP activity, and persisted, but in smaller numbers, with maturation; tertiary granules were of variable size and were negative for AP and MPO. These results demonstrated the sequential development of lysosomal enzymes during monocytic differentiation. (7 Refs)

6. FUNCTIONAL CHARACTERIZATION OF THE CELLS IN CHRONIC NEUTROPHILIC LEUKEMIA.

Dotten DA, Pruzanski W, Wong D
(c/o Pruzanski), Wellesley Hosp., 160 Wellesley St. East, Toronto, Ontario M4Y 1J3, Canada
Am J Hematol; 12(2):157-165 1982

Light and electron microscopy of neutrophils from chronic neutrophilic leukemia (CNL) did not reveal differences from normal mature neutrophils. However, functional characterization of CNL cells showed marked differences when compared to normal cells. CNL neutrophils were much less viable in suboptimal conditions. Their survival was further reduced by autologous serum and was corrected by normal human serum. CNL cells showed very active phagocytosis, but their bactericidal activity was reduced in suboptimal conditions. The total content of lysozyme and beta-glucuronidase was lower in CNL cells compared to normal neutrophils, but the release of these enzymes from stimulated cells was much higher than normal. This observation is compatible with a marked lysosomal lability. Cells from the patients' peripheral blood and bone marrow showed excessive growth in CFU-C assays. Marked susceptibility of CNL cells to cytotoxic activity of cold agglutinins, SLE sera, and CSFs was observed and may signify qualitative and/or quantitative differences in the membrane structure of CNL neutrophils, as compared to normal cells. (Author abstract) (19 Refs)

7. INTRACELLULAR LACTIC DEHYDROGENASE AND PHOSPHOHEXOSE ISOMERASE ACTIVITY IN LEUKAEMIA AND MALIGNANT LYMPHOMA.

Ho AD, Fiehn W, Hunstein W
Med. Univ. Poliklinik, Hospitalstr. 3, D-6900 Heidelberg, W. Germany
Br J Haematol; 50(4):637-645 1982

Intracellular activities of total lactic dehydrogenase (LDH) and phosphohexose isomerase (PHI) were investigated in the leukemic cells of 14 patients with acute myeloid leukemia (AML), 5 with chronic myeloid leukemia (CML), 7 with acute lymphoblastic leukemia (ALL), 19 with chronic lymphocytic leukemia (CLL), 16 with leukemic non-Hodgkin's lymphoma (NHL) and in the lymphocytes of 14 normal persons. Intracellular total LDH-activity of the blasts of AML and ALL was in the same range as the normal lymphocytes. Patients with CLL and NHL had significantly lower levels (p less than 0.01) of total intracellular LDH than the controls. Intracellular PHI activity was consistently lower in the lymphoid malignancies (ALL, CLL, NHL) than in normal lymphocytes (p less than 0.05), or in leukemic myeloblasts (p less than 0.01). The intracellular LDH/PHI index of the leukemic lymphoblasts was significantly elevated as compared to lymphocytes from normal subjects (p less than 0.0001) or to leukemic cells from patients with AML (p less than 0.001), with CLL (p less than 0.0001) or with NHL (p less than 0.001). The patients with CLL and NHL, on the other hand, had significantly lower levels of LDH/PHI ratio than the normal subjects (p less than 0.0001 and p less than 0.025 respectively). (Author abstract) (19 Refs)

8. TWO-DIMENSIONAL GEL ELECTROPHORESIS OF CELL PROTEINS OF CHILDHOOD LEUKEMIA, WITH SILVER STAINING: A PRELIMINARY REPORT.

Hanash SM, Tubergen DG, Heyn RM, Neel JV, Sandy L, Stevens GS, Rosenblum BB, Krzesicki RF
Dept. Pediatrics, Univ. Michigan, Box 66, F6515, Ann Arbor, MI, 48109
Clin Chem; 28(4,part2):1026-1030 1982

We have investigated the potential of two-dimensional electrophoresis for identifying differences in protein patterns between acute lymphocytic (ALL) and acute myelogenous leukemia (AML). We studied blood cells directly isolated from seven children with non-T, non-B ALL and five with AML. Solubilized proteins were electrophoresed with the ISO-DALT system and made visible by silver staining. More than 800 spots were routinely detected in individual gels. Patterns for multiple runs of the same sample were distinguishable. Most of the prominent spots were present in gels from all 12 of the individuals studied. However, substantial variability in spot intensity was observed, even among patients in the same group. Five spots were consistently present in gels of all the AML patients, and either completely absent or substantially decreased in ALL gels. Three other spots were present in ALL but not AML gels. We conclude that this may be a useful tool for characterizing leukemic cells. (Author abstract) (16 Refs)

9. ACUTE MONOCYTIC LEUKEMIA CHROMOSOME STUDIES.

Berger R, Bernheim A, Sigaux F, Daniel MT, Valensi F, Flandrin G
Laboratoire de Cytogenetique, Centre G. Hayem, Paris Cedex 10, France
Leuk Res; 6(1):17-26 1982

Bone marrow cells from 10 children and 24 adults with acute monocytic leukemia (24 poorly differentiated [M5a], 10 well differentiated [M5b]), were subject to cytogenetic analysis directly or after culturing without stimulation. All of the studies were performed at diagnosis, prior to treatment. Analysis consisted of G- and R-banding, and sometimes C- and Q-banding, and also cytologic identification of cells. Two patients had constitutional chromosomal abnormalities. Twelve patients (5 M5a, 7 M5b) had no abnormalities. All the remaining patients had numerical, structural, or combined abnormalities. Five patients had autosomal trisomies involving chromosomes 8, 9, 21, and 12 (?), which were also associated with structural abnormalities in another six. Twelve of the patients, mostly M5a, had structural rearrangement of chromosome 11 (at bands q22-q24 in 9, q14 in 3). Two different abnormal cell lines were seen in two patients, one at diagnosis and one at relapse. Cytologic study showed that most mitoses were seen in monocytes or monoblasts. Findings are discussed and compared to cytogenetic findings in other leukemias. (19 Refs)

10. CHRONIC T-CELL LEUKEMIAS II. CYTOGENETIC STUDIES.

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Leuk Res; 6(1):33-42 1982

Peripheral blood lymphocytes from 10 patients (7 males, 3 females; 12-76 yr old) with chronic T-cell leukemias (3 chronic lymphocytic leukemia [CLL], 6 prolymphocytic leukemia [PLL], 1 lymphosarcoma cell leukemia) were studied cytogenetically after phytohemagglutinin (PHA) stimulation. Structural and numerical abnormalities were seen in some cells from

all cases, but these were consistently clonal only in the PLL patients. The most common numerical abnormality was hypodiploidy, seen in five cases, more frequently involving loss of chromosomes 8 or 9 than others. Chromosomes most frequently involved in marker formation were 2 and 8, with a lesser frequency with 7, 9, 11, and 16. Structural rearrangements were seen in only 3/8 cases with abnormal number 8 chromosomes. No abnormalities of chromosome 14 were seen. Chromosome 2 may contain information about control of T cell proliferation, since it is often abnormal in T cell neoplasias. It is suggested that the differences in chromosomal abnormalities reported may be related to the different proliferative behavior of CLL and PLL. (22 Refs)

11. VARIANT PH1 TRANSLOCATIONS IN CML AND THEIR INCIDENCE, INCLUDING TWO CASES WITH SEQUENTIAL LYMPHOID AND MYELOID CRISIS.

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Cancer Genet Cytogenet; 5(3):187-201 1982

A serial cytogenetic study of 110 cases of chronic myelogenous leukemia (CML) has been performed with G- and/or Q-banding techniques with the following results. (1) Seven out of the 110 cases were karyotypically normal. (2) A variant Ph1 translocation was observed in three cases. (3) The frequency of Ph(1)-negative CML and that of Ph(1)-positive CML with various types of Ph1 translocation from 15 studies reported as series of 25 or more cases, including the present study, have been tabulated. The incidence of a variant Ph1 translocation was 4.1%. (4) In one case of the present study, a masked Ph1 by a translocation of material onto the short arm of the 22q- was observed in the blastic crisis but not in the chronic phase. From the present study and a review of the published cases, it appears that the incidence of such a 'masked' Ph1, which cannot be detected by conventional Giemsa staining, is less than 0.6% in CML cases. (5) The first and the second cases with a variant Ph1 translocation mentioned above developed a myeloid blastic crisis after the induction of remission of a lymphoid blastic crisis. For the present, it is unclear whether the occurrence of such blast cells in the two cases and the cytogenic findings are coincidental. However, the evidence supports the notion of 'lymphoid-myeloid' multipotentiality of certain leukemic cells. (32 Refs)

12. FREQUENCY OF PHILADELPHIA CHROMOSOME AND OTHER CHROMOSOMAL CHANGES IN ADULTS WITH CHRONIC GRANULOCYTIC LEUKEMIA.

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Arch Invest Med (Mex); 13(1):33-36 1982

Frequency of Philadelphia chromosome (PhC) and other chromosomal changes were studied in 74 patients (34 men, 40 women; 10-90 yr old) with chronic granulocytic leukemia. All the patients except one had the PhC, which was observed in all examined cells of the 63 patients and in 25-80% of examined cells of the 11 patients. Other chromosomal changes were noted in 20 patients; 8 had aneuploidy (AN), 1 had duplication of PhC (DPhC), 1 had the DPhC and a different modal number (49:XY), 3 had DPhC and AN, 2 had DPhC and polyploidy (PP), 1 had deletion, 1 had translocation and AN, and 3 had AN and PP. No correlation was evident between the chromosomal changes and survival. Longest survival was 11 yr observed in a 37 yr old woman with PhC in 100% of examined cells. Shortest survival was 40 days observed in a 22 yr old woman, who also had PhC in 100% of examined cells. Thirteen of the patients were lost, 14 died within 12 mo, 38 died within 12-72 mo, and 9 died within 72-132 mo. Majority of the patients died in blastic phase. (12 Refs) (In SPA)

13. CHROMOSOMAL, MORPHOLOGICAL AND CLINICAL CORRELATIONS IN BLASTIC CRISIS OF CHRONIC MYELOID LEUKAEMIA. A STUDY OF 69 CASES.

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Scand J Haematol; 28(2):103-117 1982

The karyotypic pattern in 69 patients with Ph1-positive chronic myeloid leukemia (CML) was investigated during the blastic phase (BC) and correlated with survival and certain parameters of potential prognostic significance, including blast morphology, basophilia and thrombocytopenia. There was no difference in median survival in BC between patients with and without aberrations in addition to the Ph1. Nor were there any differences in this respect among patients with the specific aberrations +Ph1, +8, iso(17q), or other abnormalities. There was no correlation between the incidence of thrombocytopenia and any particular karyotypic change. However, the incidence of basophilia was a characteristic feature for patients with an iso(17q). The survival time in BC was considerably longer in patients with a lymphoid morphology of the blastic cells compared to the myeloid varieties, and within the myeloid varieties the survival in BC was longer in patients with granular differentiated blasts than in those with granular atypical blast cells. No obvious correlation was apparent between blast morphology and karyotypic pattern. However, a pattern was discernible regarding survival and certain chromosomal changes within some morphologic groups: in patients with granular differentiated and lymphoid morphology, the median survival in BC was considerably longer when the bone marrow cells had a Ph1 as the sole abnormality compared to patients who had additional aberrations. (Author abstract) (22 Refs)

14. EXTRA CHROMOSOME 12 AND PROGNOSIS IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

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Scand J Haematol; 28(2):163-168 1982

Peripheral blood lymphocytes from 22 consecutive patients with chronic lymphocytic leukemia were stimulated with the polyclonal B-cell mitogens lipopolysaccharide from E coli (LPS) and Epstein-Barr virus (EBV). Stimulation was successful for chromosome analysis in 14 patients. Eleven patients had chromosomal aberrations and 7 of these had an extra chromosome 12. In two patients an extra chromosome 12 was the only abnormality, while additional aberrations were found in five patients. Three patients had complex aberrations involving deletion of chromosome 6. One of these patients also had a translocation between chromosomes 12 and 14. One patient had a translocation between chromosomes 11 and 14. In three patients no aberrations were detected. The time elapsing between diagnosis and appearance of clinical symptoms which were indications for treatment was significantly shorter in patients with an extra chromosome 12 than in those without this abnormality. Thus, it appears that an extra chromosome 12 is associ-

ated with a more rapid course of the disease, and may therefore be of importance for the prediction of prognosis. (Author abstract) (10 Refs)

15. ACUTE LYMPHOCYTIC LEUKEMIA: BIOLOGICAL MARKERS OF CLINICAL RESPONSE.

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J Cell Physiol; Suppl1:127-132 1982

New biological observations that have clinical importance in the treatment of acute lymphoblastic leukemia (ALL) are presented, and current therapeutic problems are described. One hundred and thirty-five patients were entered into the treatment program for standard-risk patients; 101 had WBC counts less than 25,000/cubic mm (mm3) and none of those patients have relapsed. Nine of 34 patients with counts greater than 25,000/mm3 have already relapsed. Proliferative activity was assessed by determining the tritiated thymidine labeling index of blood and bone marrow leukemic blast cells. A significant difference in treatment outcome was found when the group of patients was divided into two parts based on higher or lower level of proliferative activity in the blood and bone marrow blast cells. Bone marrow treatment failed in 42% of patients with labeling index (LI) less than 6%, and in 74% of patients with LI greater than 6%. Initial blast cell karyotypes of 135 patients with ALL were analyzed. The patients with greater than 50 chromosomes have had only two treatment failures. Only 70% of 28 patients with pseudodiploid karyotypes achieved initial remission and 19 have experienced treatment failure. Leukemic blast cell DNA content was analyzed by flow microfluorometry and the data was correlated with the results of the cell surface marker studies. Cells having hyperdiploid DNA content were more likely to have an expression of surface common ALL antigen. However, those cells having T-lymphocyte markers rarely have abnormal DNA content detectable by flow cytometry. These observations suggest the existence of an interrelationship among studied biological features associated with treatment response. (12 Refs)

16. FIBRINOLYTIC ACTIVITY IN NORMAL AND LEUKEMIC MYELOID DIFFERENTIATION.

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Haematologica (Pavia); 67(1):17-22 1982

Fibrinolytic activity was measured in normal myeloid and chronic myeloid leukemia (CML) cells and compared by stage of differentiation. Cells were fractionated on a discontinuous bovine serum albumin gradient, with the more dense cells being more differentiated. Fibrinolytic activity was measured using 125I-fibrin plates, and divided into total and non-plasmin-mediated activity. Both cell types were separated by the gradient, with the CML cells showing a better enrichment of myeloid cells at all densities because of the lesser number of erythroblasts. Both cell types had progressively increasing fibrinolytic activity with increasing fraction density and thus increasing differentiation. The correlation coefficients between the normal and CML cells were 0.89 (p less than 0.01) and 0.78 (p less than 0.01) for total and non-plasmin-mediated activities, respectively. CML does not appear to affect the development of cellular fibrinolytic activity. The use of this assay for examining myeloid differentiation is discussed. (14 Refs)

17. MEGALOBLASTIC DISTURBANCE OF MATURATION OF ERYTHROPOIESIS IN PLASMOCYTOMA AND IN CHRONIC LYMPHATIC LEUKEMIA.

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Z Gesamte Inn Med; 37(3):91-93 1982

Of fifty-seven untreated patients (34 men, 23 women; 5 were less than 50 yr, 37 were 50-70 yr, and 15 were greater than 70 yr old), 52 with plasmocytoma (PC), and 5 with Waldenstrom's macroglobulinemia (WMG), underwent evaluation of erythropoiesis (EP). The EP was increased in 11, normal in 9, decreased in 28, and almost absent in 9. Normal erythroblasts were often associated with disturbances of maturation (DM). DM were observed in 26/52 patients (15 men, 11 women) with PC, and 13 of them exhibited significant changes. DM was observed in 3/5 patients with WMG and two of them had significant changes. DM was not related to the age of the patients, but it increased with the increasing polymorphism of the PC cells. The EP was evaluated also in 46 untreated patients (25 men, 21 women; 4 were less than 50 yr, 20 were 50-70 yr, and 22 were greater than 70 yr old) with chronic lymphatic leukemia (CLL). The EP was increased in 13 patients, normal in 10, decreased in 9, and strongly decreased in 14. Of the 46 patients with CLL, the DM were significant in 13 (none, very little, or normal EP), considerable in 13 (some normal EP), and negligible in 9. The DM were more pronounced in the patients with CLL. (13 Refs) (In GER)

18. ERYTHROPOIESIS IN HAIRY CELL LEUKAEMIA: A TRUE ERYTHROID FAILURE.

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Scand J Haematol; 28(2):97-102 1982

A quantitative evaluation of erythropoiesis was carried out in 12 patients with hairy cell leukemia (HCL). The results were compared with those obtained in eight patients with aplastic anemia (AA) in order to define the characteristics of erythroid failure in HCL. Discriminant analysis was applied to both hematological and erythrokinetic parameters of the two disease groups. Plasma iron concentration and MCV were significantly higher in AA, and allowed a perfect separation of the patients. As regards erythrokinetics, values of ineffective erythropoiesis and peripheral hemolysis were able to separate completely the two disease groups, being significantly lower in HCL than in AA. A true erythroid failure was the peculiar erythrokinetic pattern of HCL. This conclusion allows one to speculate on the nature of the stem cell damage in this disease. (Author abstract) (19 Refs)

19. CHARACTERIZATION OF HEMOPOIETIC PRECURSOR CELLS IN JUVENILE-TYPE CHRONIC MYELOCYTIC LEUKEMIA.

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Leuk Res; 6(1):43-53 1982

Bone marrow (BM) and peripheral blood (PB) cells from three children (all males, 8 mo to 1 yr 11 mo of age) with juvenile-type chronic myelocytic leukemia (CML) were examined for colony-forming capacity and colony composition using a new whole culture staining cytochemical technique. Granulo-

cyte (G-CFC) and especially macrophage colony-forming cells (M-CFC) were increased in GM and PB. In addition, erythroid colony-forming cells were increased in PB. Removal of cells phagocytizing carbonyl iron or adherent to glass greatly reduced the numbers of M-CFC, suggesting that some of the M-CFC may have phagocytic and/or adherent activity. Radiation sensitivity and DNA synthesis as measured by thymidine suicide were not significantly different for the G- and M-CFC. Colony-stimulating activity from the CML cells on normal BM cells was predominantly directed towards granulocytes, indicating that the predominance of M-CFC was not due to changes in humoral regulation. These results are contrasted to findings in adult-type, Philadelphia chromosome-positive CML, in which granulocyte colonies predominate. (21 Refs)

20. ACUTE MYELOID LEUKEMIA COLONY GROWTH IN VITRO: DIFFERENCES OF COLONY-FORMING CELLS IN PHA-SUPPLEMENTED AND STANDARD LEUKOCYTE FEEDER CULTURES.

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Blood; 59(4):816-821 1982

Bone marrow or blood of patients with acute myeloid leukemia was subjected to cell separation and the cells investigated for in vitro colony growth. Discontinuous albumin density gradient centrifugation and depletion of E-rosette-forming cells resulted in purified fractions of acute myeloid leukemia cells. From these fractions, growth of large leukemic colonies was obtained in the PHA-leukocyte feeder (PHA-LF) colony technique in 12 of 14 patients. The standard double agar layer technique with a leukocyte feeder for granulocyte-macrophage colony forming cells (GM-CFC) supported colony formation in only four cases. The PHA-LF leukemic colony-forming cells (CFC) were found to be of low buoyant density (always less than or equal to 1.062 g/ml-1) when compared to normal marrow GM-CFC (peak at 1.065t g/ml-1). The density profile of PHA-LF CFC paralleled the distribution of the nucleated cells in eight cases, but in four patients, the CFC peak was found at a distinctly lower density; this suggested that a specific leukemic subpopulation had a colony-forming capacity. In three of of the four patients with colony growth in the double layer agar technique, it was evident that these CFC had density properties different from those of PHA-LF CFC. These findings suggest that cells giving rise to large colonies in the PHA-LF and double layer agar assays represent distinct leukemic subpopulations. (Author abstract) (24 Refs)

21. AGAR CULTURE OF BONE MARROW CELLS IN ACUTE MYELOID LEUKEMIA AND DYSMYELOPOIETIC SYNDROMES. REEVALUATION OF ITS PROGNOSTIC VALUE.

Coiffier B, Bryon PA, Fiere D, Felman P, Gentilhomme O, Van HV, Viala JJ, Germain D
Laboratoire Central d'Hematologie, Hopital E.-Herriot, F-69374 Lyon Cedex 2, France
Nouv Rev Fr Hematol; 24(1):13-18 1982

Results obtained in in vitro bone marrow cell culture were expressed per ml of aspirated marrow instead of per 10(5) nucleated cells plated. In 41 patients with acute myeloid leukemia four types of growth were found. Three types exhibited hypercellular marrow, microclusters, isolated cells, or macroclusters, and complete remission rates of 86, 63, and 14%, respectively. No remissions occurred in the fourth type with relatively hypocellular marrow. In 79 patients with dysmyelopoietic syndrome, three groups could be distinguished on the basis of in vitro growth and the number of nucleated cells per ml of marrow: subnormal, decreased, and leukemic. Hematological studies of patients within these three groups showed no significant differences. Outcomes in the patients varied widely. Incidence of deaths in the three groups was 20/23, 17/35, and 12/21, respectively. In the leukemic group death occurred after a leukemic phase; such was not the case in patients with decreased growth. No significant differences were seen among the groups as regards sideroblastic anemia, refractory anemia with or without excess blasts, and subacute myelomonocytic leukemia. In some patients, two or more cultures were studied. Among 10 patients initially with subnormal growth, 8 maintained the same pattern. Those with a decreased growth showed aggravation of the profile with a trend toward absence of growth. Two profiles were seen in the leukemic group: persistance of the same growth (8/15) or absence of growth (7/15). (26 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

22. ACUTE MONOCYTIC LEUKEMIA: A SURFACE MARKER STUDY.

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Am J Hematol; 12(2):139-147 1982

Thirteen cases of acute monocytic leukemia (AMoL) were studied morphologically, cytochemically, and immunologically in an attempt to determine similarities and/or differences between acute monocytic and lymphocytic leukemias. Single class surface immunoglobulins (IgG kappa) were seen in six cases. These markers are thought to represent serum immunoglobulins attached to the leukemic monocytes via the receptors for the Fc portion of immunoglobulin and are not synthesized by the cells as is the case with B lymphocytes. Receptors for complement were also noted. It appears that surface immunoglobulins and receptors for the Fc portion of the immunoglobulin and complement, which are found on several classes of normal lymphocytes and monocytes, may also be found on leukemic monocytes. Antisera to B lymphocytes, detecting HLA-DRw antigens, also reacted with some of the leukemic monocytes. (Author abstract) (34 Refs)

23. HLA ANTIGENS AND DURATION OF SURVIVAL OF PATIENTS WITH HYPOPLASTIC ANEMIA AND ACUTE LEUKEMIAS.

Fainshtein FG, Tananov AT, Turbina NS, Isaev VG, Abakumov EM, Zaitseva GA, Kut'ina RM, Belonogova TS
First Hematological Dept., Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Probl Gematol Pereliv Krovi; 27(2):7-11 1982

Prognostic value of HLA phenotype was studied in 100 patients with acute lymphoblastic leukemia (ALL), 100 with acute myeloblastic leukemia (AML), and 100 with hypoplastic anemia (HA). Analysis of the distribution of HLA antigens showed significant decrease of the frequences of A1, B8, and B14 antigens in ALL patients (14%, 5%, and 2%, respectively, compared with 26.1%, 16.1%, and 8.3%, respectively, in controls) and significant increase of the frequences of B12 and B7

antigens in HA patients (31% and 41%, respectively, compared with 13.3% and 25%, respectively, in controls). Distribution of HLA antigens in AML patients did not differ from that in controls. To evaluate the relationship between the duration of survival and HLA antigens, the patients were divided into two groups. Group 1 included HA and ALL patients who survived for less than 2 yr and AML patients who survived for less than 1 yr. Group 2 consisted of HA and ALL patients who survived for greater than 2 yr and AML patients who survived for greater than 1 yr. The ALL and AML patients in Group 2 had significant increase of the frequency of A2 antigen (82.9% and 63.6%, respectively, compared with 42.2% and 30.5%, respectively, in Group 1). The frequency of A1 antigen in ALL and AML patients showed progressive decrease with the increase of the duration of survival (23.7% and 44.4% in Group 1, compared with 5.7% and 15.2% in Group 2). HA patients in Group 1 were characterized by increased frequency of B27 and B5 antigens, while HA patients in Group 2 showed significant increase of the frequency of B12 antigen. (3 Refs) (In RUS)

24. A HUMAN T-CELL ANTIGEN DEFINED BY XENOANTISERUM TO SEZARY LEUKEMIC CELLS: IMMUNOCHEMICAL AND FUNCTIONAL STUDIES.

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Am J Hematol; 12(2):95-107 1982

Xenoantiserum to Sezary cell leukemia cells (ASS) was developed by immunizing rabbits with those cells and was absorbed with human red cells, liver, tonsil B cells, and cultured Raji cells. This reagent reacted by immunofluorescence with virtually all human thymus and T cells. In the thymus, medullary cells reacted more strongly with ASS than did cortical thymocytes. When immunoprecipitates that formed between ASS and 125I-labeled lymphocyte surface glycoproteins were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, it was found that ASS precipitated a 72K mol wt (MW) glycoprotein from T cells but not from B cells. On the other hand, it was shown by functional studies that T cells sensitive to the cytotoxic effect of ASS contained T cells that could aid the immunoglobulin synthesis of B cells induced by pokeweed mitogen. On the other hand, suppressor T cells induced by concanavalin A resided in those cells rather resistant to its cytotoxic effect. These data support the idea that the 72K MW glycoprotein on human thymus and T cells might be homologous to mouse Lyt-1 antigens. (Author abstract) (27 Refs)

25. ANALYSIS OF CARBOHYDRATE DETERMINANTS ON MEMBRANES OF LEUKEMIC LEUKOCYTES USING NATURALLY OCCURRING MONOCLONAL HUMAN ANTIBODIES (COLD AGGLUTININS).

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Protides Biol Fluid Proc Colloq; 29:623-626 1982

The reaction of monoclonal anti-I, -i, -Pr1, -Pr2, -Gd and the monoclonal cold agglutinin (CA) Sa with cells from patients with acute leukemia was examined. The RBC-autoantigens I, i, Pr1, Pr2, GD and SA were found on blasts of 25 adult patients with acute leukemia [10 myelocytic (AML), 2 promyelocytic, 4 myelomonocytic (AMML), and 9 lymphoblastic (ALL)]. Expression of three antigens was associated with the cell type of leukemia: I, i, and Pr1 were not detectable or only weakly expressed on AML cells, whereas on ALL cells the antigens occurred to a greater extent. There was, however, considerable heterogeneity in the ALL group. The proportion of stained cells was often less than 30%. The difference in the anti-i reaction between AML and ALL was less striking after neuraminidase treatment, indicating that more antigenic determinants became available by enzymatic removal of N-acetyl-neuraminic acid. In contrast to AML cells, there was a very strong reactivity of anti-I, anti-i, and anti-Pr1 with AMML cells. Since it is often difficult to distinguish AMML and AML morphologically, the CA may be useful. No correlation with cell type was found in the case of Pr2, Gd, and Sa. Study of cultured PHA-stimulated T lymphocytes revealed that the antigen expression varied concomitantly with the culture periods. The results suggested that i, Gd, and Sa, in contrast to Pr1, are preferentially expressed on proliferating cells. (8 Refs)

26. 'TARGET' CELLS, CELLULAR PHENOTYPES, AND LINEAGE FIDELITY IN HUMAN LEUKAEMIA.

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J Cell Physiol; Suppl1:113-125 1982

Features of leukemic phenotypes in relation to normal hemopoietic differentiation were investigated in a study developed as a part of a routine immunodiagnostic service for leukemia in the United Kingdom (UK). Leukemic samples (heparinized blood, lymph node biopsies, cerebrospinal fluid, and peritoneal aspirates) were obtained from referring hospitals throughout the UK. A presumptive normal sequence of antigen (and other marker) expression in T cell differentiation is presented. The scheme is based upon reported antigenic heterogeneity of cortical and medullary thymocytes and subsets of blood T cells. The corresponding maturation 'positions' of 95 leukemic T cell phenotypes analyzed are presented. T-acute lymphoblastic leukemia (T-ALL), and T-non-Hodgkin's lymphoma in childhood 'correspond' to early or late thymocyte populations while T cell leukemias or lymphomas of older (greater than 35 yr) patients diagnosed as cutaneous lymphoma or leukemia, chronic lymphocytic leukemia, prolymphoblastic leukemia, or lymphoblastic lymphoma, all had 'mature' T phenotypes. The phenotypes that were documented in non-T-ALL are summarized. The majority of complementary ALL that do not synthesize detectable mu chain nevertheless have rearranged mu chain genes as revealed by molecular hybridization studies. Alterations in phenotype during leukemia progression or relapse may provide some evidence for distortion of 'normal' genetic programs as well as revealing the lineage affiliations of various clonogenic populations. Alterations in the latter population may indirectly indicate the possible target cell population involved. (89 Refs)

27. IMMUNOLOGIC EVALUATION OF T CHRONIC LYMPHOCYTE LEUKEMIA CELLS: CORRELATIONS AMONG PHENOTYPE, FUNCTIONAL ACTIVITIES, AND MORPHOLOGY.

Pandolfi F, De Rossi G, Semenzato G, Quinti I, Ranucci A, De Sanctis G, Lopez M, Gasparotto G, Aiuti F
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Blood; 59(4):688-695 1982

Chronic lymphocytic leukemia of T-cell origin (T-CLL), a rare variant of CLL, appears to be a clonal proliferation of mature T cells of one of several subsets. In the cells of seven T-CLL patients, surface markers (including those reacting with a panel of monoclonal antibodies), functional activities, and electron microscopic morphology were evaluated. The pheno-

typic patterns of circulating T-CLL cells correspond to those of normal mature T-cell subsets. The cells of three patients demonstrated at least one marker reported to be expressed by suppressor/cytotoxic T cells; those of three patients expressed markers apparently linked with T-helper activity. Cells from one patient appeared to be a heterogeneous proliferation of more than one T-cell subset. These T-Cll cells may also retain some of the functional activity of the normal T subpopulations. Our data indicate that a combination of several tests should be used to characterize the proliferating cells in T-CLL. (Author abstract) (29 Refs)

28. PROTEIN A REACTIVITY OF LYMPHOCYTES FROM SOME PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA MEDIATED BY AN INTERACTION WITH THE F(AB')2 REGION OF SURFACE IMMUNOGLOBULIN.

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Scand J Immunol; 15(3):287-295 1982

Peripheral blood lymphocytes (PBL) from 15 of 38 patients with chronic lymphocytic leukemia (CLL) were capable of forming rosettes with human erythrocytes coated with staphylococcal protein A (SpA-HRBC). PBL from seven patients also showed a marked proliferative response after stimulation with Staphylococcus aureus bacteria strain Cowan I (Cowan Staph). The SpA-rosetting of CLL cells was inhibited by incubation with F(ab')2 fragments of anti-immunoglobulin (Ig) antibodies. In addition, incubation with these fragments inhibited the proliferative response of leukemic B cells to Cowan Staph. The Cowan-Staph-induced proliferation of CLL cells was also impaired by the addition of normal human IgG and human IgG F(ab')2 fragments to the cultures, whereas non-immune rabbit IgG was not inhibitory. The inhibitory activity of human IgG F(ab')2 fragments was retained by a SpA-Sepharose column, and it was found in the material recovered from the same column by acid elution. These data indicate that an interaction between SpA and a structure located in the F(ab')2 region of surface Ig of different classes is responsible for either SpA-binding or the Cowan-Staph-induced proliferative response of PBL from some patients with CLL. (Author abstract) (24 Refs)

CHEMOTHERAPY

29. THERAPY OF ACUTE MONOBLASTIC LEUKEMIA.

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Service d'Oncologie Medicale, Groupe Hopitalier, Pitie Salpetriere, 47 Boulevard de l'Hopital, 75013 Paris, France
Haematol Blood Transfus; 27:189-194 1981

Treatment of 84 patients with acute monoblastic leukemia is reported. Three received prednisone, 6-mercaptopurine, and hydroxyurea; 81, anthracyclines; 18, daunorubicin (DAU), 55, rubidazone (RUB); 4, the combination of RUB, cytosine arabinoside (Ara C), and VP 16; and 4, the combination of RUB, Ara C, and vincristine. Forty-one patients also underwent CNS prophylactic irradiation when hematologic remission was achieved. Complete remission (CR) was achieved in 58 patients (72%), 13 patients failed, and 13 died in aplasia. Of the 18 patients treated with DAU, 9 achieved CR, 3 failed, and 6 died during induction. Of the 55 treated with RUB, 42 (76%) achieved CR, 8 failed, and 5 died during induction. Seven of the eight patients treated with combinations containing RUB achieved CR. None of the three patients treated without anthracyclines achieved CR and all died during induction. Median duration of the 58 with CR was 195 days. Median duration of CR was 65 days for those treated with DAU, 167 for those treated with RUB, and 254 for those treated with RUB plus CNS irradiation; these figures for the three groups were not statistically significant. Duration of CR was influenced by WBC count, but not by age, sex, or tumoral syndrome. Relapses occurred in 35/58 patients who achieved CR; 21 in the bone marrow, 6 in the CNS, and 5 in the skin. No meningeal relapses occurred in patients given prophylactic CNS irradiation. (25 Refs)

30. SHORT-TERM TREATMENT FOR ACUTE MYELOGENOUS LEUKAEMIA.

Bell R, Rohatiner AZ, Slevin ML, Ford JM, Dhaliwal HS, Henry G, Birkhead BG, Amess JA, Malpas JS, Lister TA
Section Medical Oncology, Univ. Hosp., Boston, MA, 02118
Br Med J; 284(6324):1221-1224 1982

Short-term treatment with doxorubicin, cytarabine, and 6-thioguanine was given to 91 consecutive adults with acute myelogenous leukemia. Fifty patients received high doses (regimen I) and 41 very high doses (regimen II). Where possible, six treatment cycles were given (total dose of doxorubicin 450 mg/m(2)) regardless of the number of cycles required to achieve complete remission. No additional treatment was given. The remission rate was significantly higher with regimen I than with regimen II (34/50 compared with 15/41, p less than 0.01), the latter, more intensive regimen being associated with a greater incidence of fatal infection (13/41 compared with 5/50, p less than 0.01). Duration of remission was, however, significantly longer with regimen II (p less than 0.05); the median has not yet been reached after a minimum follow-up of two years. Intensive short-term treatment is a feasible strategy for the treatment of acute myelogenous leukemia. (Author abstract) (18 Refs)

31. COMBINATION CHEMOTHERAPY FOR ACUTE LYMPHOCYTIC LEUKAEMIA IN 25 ADULTS.

de Vries EG, Mulder NH, Houwen B, Haaxma-Reiche H
Div. Hematology, Dept. Medicine, Univ. Hosp., Oostersingel 59, 9713 EZ Groningen, The Netherlands
Blut; 44(3):151-158 1982

Sixteen male and 9 female patients (15-48 yr old) with acute lymphocytic leukemia were treated with three weekly cycles of vincristine (VC) and prednisone (PN). Thirteen patients received up to five weekly doses of daunorubicin when the VC-PN treatment was inadequate. Three patients who still failed to respond were given one or two courses of cytosine arabinoside (CA), 6-thioguanine (TG), and adriamycin (AM) with success. Maintenance therapy consisted of 36 mo of VC, PN, methotrexate, and 6-mercaptopurine. Relapse after 18 mo of remission was treated as primary induction; before 18 mo the CA-TG-AM treatment was used. The median remission period was 19 mo, and the median survival duration was 38 mo. The quality of life of the patients was rated good. The seven patients presenting with a mediastinal mass (treated with nitrogen mustard and radiation as necessary) had a significantly shorter period of remission than those without masses. Of the 15 patients who relapsed (13 in bone marrow), 7 relapsed twice. Prognosis in retreatment with VC-PN was better than with CA-TG-AM. Treatment of two subjects also presenting with

CNS leukemia and six subsequently developing the disease is discussed. (19 Refs)

32. IMMUNOLOGICAL EVALUATION OF 22 PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA OFF-THERAPY: A LONGITUDINAL FOLLOW-UP.

Pasino M, Vadala R, DeBernardi B, Comelli A, Mori PG, Dini G, Bisogni MC, Tonini GP, Massimo L
(c/o Massimo) Dept. Pediatric Hematology and Oncology, Giannina Gaslini Inst., Via 5 Maggio 39, I-16148 Genova, Italy
Helv Paediatr Acta; 36(1):69-80 1981

Immune function was studied for 3-42 mo (median 10 mo) after the end of therapy in 22 children (1.5-9 yr old at diagnosis) with acute lymphoblastic leukemia who remained in complete remission during 3 yr of treatment and after the end of treatment. In 8/22 patients, induction therapy consisted of vincristine (VCR), prednisone (PRN), and CNS irradiation (2,400 rads), followed by the L-2 protocol. The other 14 patients were given the IGG-74 protocol: induction with VCR, PRN, L-asparaginase cytoxan (CTX), adriamycin (ADR), intrathecal (ith) cytosine arabinoside (araC), ith methotrexate (MTX), and iv araC; followed by repeated maintenance courses of 6-mercaptopurine, MTX (ith and po), ADR, CTX, VCR, PRN, and carmustine. The effects of the two protocols on immune function were not significantly different. Major deficiencies of T lymphocyte numbers and responses to blastogens (phytohemagglutinin and concanavalin A; pokeweed mitogen responses declined only slightly) were observed in the first 12 mo after the end of treatment, but no significant changes in the B lymphocytes or serum IgM, IgG, or IgA levels were observed. Immunologic recovery was often characterized by a remarkable rebound at 15-18 mo. The immunosuppressive effects of intensive chemotherapy seemed to be transient, mainly limited to the first 3 mo. Almost all patients achieved immunologic reconstitution within 1 yr after the end of therapy. (22 Refs)

33. GROWTH CHARACTERISTICS OF LEUKEMIC AND NORMAL HEMATOPOIETIC CELLS IN PH' + CHRONIC MYELOGENOUS LEUKEMIA AND EFFECTS OF INTENSIVE TREATMENT.

Goto T, Nishikori M, Arlin Z, Gee T, Kempin S, Burchenal J, Strife A, Wisniewski D, Lambek C, Little C, Jhanwar S, Chaganti R, Clarkson B
(c/o Clarkson), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 59(4):793-808 1982

The proliferative and differentiation characteristics of leukemic cells from chronic phase (Ph' +) CML were examined in vitro and compared to those of hematopoietic precursors from normal individuals. The rates of proliferation and differentiation of the leukemic and normal precursors were very similar and only minor differences were discerned. Serial direct cytogenetic analyses of fresh marrow aspirations were performed on 28 patients with early Ph' + CML prior to and during treatment with an intensive combination chemotherapy regimen (L-15 protocol, which includes; cytosine arabinoside, cyclophosphamide, daunomycin, hydroxyurea, methotrexate, 6-thioguanine, vincristine, prednisolone, busulphan and 6-mercaptopurine), which destroyed a large fraction of the leukemic population and permitted repopulation of the marrow with predominantly Ph'-negative cells in about half of the patients. However, most of the complete remissions were of short duration. Even when no Ph' + cells were found on direct cytogenetic preparations of fresh marrow aspirates, some Ph' + metaphases were invariably found in cells arising from cultures of the core marrow biopsies and/or in colonies arising from concentrated marrow large cell fractions obtained by cell separation procedures. In several patients prior to treatment with the L-15 protocol, a significant percentage of Ph'-negative metaphases were found in colonies arising from blood small cell fractions, while the direct marrow cytogenetic analysis showed only Ph' + metaphases. It is concluded that only subtle differences exist between the normal and leukemic cells, and it is doubtful if it will be possible to selectively eradicate the leukemic population with currently available chemotherapeutic agents without encountering fatalities due to destruction of residual normal stem cells. (Author abstract) (60 Refs)

34. PREDICTIVE VALUE OF THE CFU-C ASSAY IN ACUTE NONLYMPHOCYTIC LEUKEMIA.

Kirshner JJ, Goldberg J, Nelson DA, Gottlieb AJ
(c/o Goldberg), Dept. Medicine, Section Hematology, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210
Am J Med; 72(4):615-619 1982

A double-layer agar culture assay for granulopoietic progenitor cells (CFU-C) was employed to study the in vitro growth pattern of bone marrow or peripheral blood cells from 37 patients at diagnosis of acute nonlymphocytic leukemia. The patients were classified as having Type A growth if there were greater than 50 colonies (A1), or greater than 1 colony and greater than 50 clusters was observed after 14 days in culture (A2). Type B growth was defined as no growth (B1), less than 50 colonies and less than 50 cluster (B2) or cluster growth only (B3). Agar cultures containing marrow cells from 10 patients were stained in situ, and the colonies and clusters revealed abnormal cellular maturation. Treatment with cytosine arabinoside and an anthracycline resulted in a complete remission of leukemia in 1 of 15 patients with Type A growth and 17 of 22 patients with Type B growth. The subtype of growth pattern did not correlate with the mechanism (ie drug resistance versus kinetic resistance) for the failure to achieve a complete remission. The subtype of Type B growth (B1, B2 or B3) did not correlate with the duration of complete remission. Nonetheless, the growth patterns observed in cultures of cells obtained from patients with acute nonlymphocytic leukemia appear to be excellent predictors of the success of achieving complete remission with induction therapy. (Author abstract) (21 Refs)

SUPPORTIVE CARE

35. BONE MARROW TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES.

Blume KG, Forman SJ
City of Hope Bone Marrow Transplant Group, City of Hope Natl. Medical Center, Duarte, CA, 91010
J Cell Physiol; Suppl1:99-102 1982

Marrow transplantation results obtained with patients suffering from acute myelogenous leukemia (AML), acute lymphoblastic leukemia, chronic granulocytic leukemia (CGL), and acute malignant myelosclerosis (AMMS) are discussed. Bone marrow transplantation (BMT) was performed for patients with AML who were in complete first remission. Actuarial disease-free survival for such patients is in the order of 60% with a follow-up time reaching 5 yr. The incidence of recurrence for those patients is approx 10% with most relapses occurring during the first post-transplant yr. The first promising results using BMT in CGL was a series of patients who were grafted from identical twin donors while they were still in the

chronic phase of their disease. The Philadelphia chromosome was abrogated in the majority of the patients and no further therapy has been required. This series has been extended to more than 15 patients and relapse-free survival is over 75%. A response to chemotherapy in AMMS is almost never attained and the patients die within weeks or months after diagnosis has been established. Six patients with AMMS have undergone allogeneic BMT and three patients have become disease-free, long-term survivors. Based on previous fibroblast culture studies, the fibrosis/sclerosis of the marrow is a reactive phenomenon secondary to the proliferation of the abnormal hemopoietic cell clone. Only 20 patients with non-Hodgkin's lymphoma who were refractory to conventional management have been treated with marrow ablative therapy followed by marrow grafting. Nine patients have survived without recurrent lymphoma for 1-10 yr. (18 Refs)

36. BONE MARROW TRANSPLANTATION FOR LEUKEMIA AND APLASTIC ANEMIA: MANAGEMENT OF ABO INCOMPATIBILITY.

Curtis JE, Messner HA
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Can Med Assoc J; 126(6):649-655 1982

Between February 1971 and October 1980, 34 patients with leukemia or aplastic anemia received bone marrow transplants from HLA-identical siblings whose lymphocytes did not react in a mixed leukocyte culture. The donors of 10 patients were ABO-incompatible, and for five pairs the ABO incompatibility was major. Plasma exchanges followed by a red blood cell exchange transfusion reduced the anti-A titers to 1:4 or less in these patients. The ABO incompatibility had no adverse effect on the results of marrow transplantation. Twenty-two patients, including 16 of the 20 who received their transplant after January 1, 1980, are still living. Seven of the 15 patients with acute leukemia have survived 89 to 466 days, and 4 of the 6 with chronic myelogenous leukemia (CML) have survived 117 to 545 days. Of the 13 patients with aplastic anemia, 11 are alive up to 8 years after transplantation. Marrow transplantation, when possible, is the treatment of choice for young patients with acute leukemia in remission and for patients with aplastic anemia. Marrow transplantation may also prove to be effective in patients with CML. (Author abstract) (24 Refs)

37. THE ROLE OF MARROW TRANSPLANTATION IN THE ERADICATION OF MALIGNANT DISEASE.

Thomas ED
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cancer; 49(10):1963-1969 1982

Use of bone marrow transplants (BMT) in the treatment of leukemia is reviewed. Experimental results of BMT in dogs indicated the value of total body irradiation (TBI), ability to store marrow at low temperature, capacity of stem cells from the buffy coat to repopulate irradiated bone marrow, sensitizing ability of blood transfusion, prevention of graft-vs-host disease (GVHD) by methotrexate therapy, importance of histocompatibility, and establishment of healthy chimera. Of 126 patients with acute leukemia treated with BMT following relapse, 13/110 allogeneic graft recipients and 6/16 syngeneic recipients were alive 6-11 yr after grafting. TBI was administered prior to grafting. Deaths resulted from advanced illness, GVHD, and relapse. In 22 acute lymphoblastic leukemia patients in second relapse who underwent BMT, all grafts were successful and only 3 patients died of nonleukemic causes in the first 100 days after grafting. The principal problem was leukemia recurrence. Eleven of 19 acute nonlymphoblastic leukemia patients receiving BMT were alive 3.5-5.5 yr postgrafting. BMT in chronic granulocytic leukemia patients during chronic or blast phases are described. The two major problems associated with BMT are discussed: death from nonleukemic causes such as GVHD and/or opportunistic infection, and death from leukemia recurrence. Anti-thymocyte globulin has been administered to some patients in an attempt to prevent acute GVHD. Chronic GVHD is discussed. A particular problem is interstitial pneumonia which may be due to Pneumocystis carinii or cytomegalovirus infection. Several hypotheses are present to explain the recurrence of leukemia in donor-type cells. (52 Refs)

38. EXPERIENCES OF 16 CHILDREN TREATED WITH BONE MARROW TRANSPLANTATION.

Hoshi Y, Johnson FL
Dept. Pediatrics, Jikei Univ. Sch. Medicine, Tokyo, Japan
Rinsho Ketsueki; 22(12):1909-1915 1981

Sixteen children (9 males, 7 females; 1-17 yr old; 5 with acute lymphocytic leukemia, ALL; 7 with acute non-lymphocytic leukemia, ANLL; 2 with non-Hodgkin's lymphoma; 1 with neuroblastoma; 1 with aplastic anemia, AA) were observed for more than 102 days after receiving allogeneic bone marrow transplantation. No graft rejection occurred, and 11 patients (69%) survived without complications for more than 4-10 mo after receiving grafts. Four patients (2 ALL, 1 ANLL, and 1 neuroblastoma) relapsed, and one patient each of ALL and neuroblastoma died of the respective disease. One case each of ALL and ANLL received chemotherapy and remission was still maintained. Ten patients (63%) had mild to severe graft-versus-host disease (GVHD), 7 patients (44%) needed therapy such as prednisolone, and 3 patients (19%) died of severe GVHD accompanied by infection. Four of six patients without GVHD relapsed, while none with GVHD relapsed. All patients required platelet transfusion, and two patients with severe GVHD accompanied by Staphylococcus infection were transfused with packed red blood cells. Twelve patients had fever and received antibiotics: significant bacteria were detected in six patients. Among the six infected, two died, and the other four improved with antibiotics. It appears that transplantation should be performed during remission rather than after relapse, and at a relatively earlier period rather than at a later, more advanced stage. (18 Refs) (In JPN)

39. THERAPEUTIC LEUKAPHERESIS IN HAIRY CELL LEUKEMIA.

Mielke CH, Dobbs CE, Winkler CF, Yam LT
Inst. Medical Sciences, Pacific Medical Center, PO Box 7999, San Francisco, CA, 94120
Arch Intern Med; 142(4):700-702 1982

Therapeutic leukapheresis was performed on three patients, and plasmapheresis on two patients with far-advanced hairy cell leukemia. Two of the three patients who were treated with leukapheresis had many hairy cells in their peripheral blood, while the other had relatively few. In each patient, dramatic clinical and hematologic improvements were observed that have sustained for more than 23, 10, and 26 mo, respectively. Plasmapheresis of similar intensity failed to show any appreciable therapeutic effects on two other patients with similar clinical and hematologic findings. We believe that the favorable therapeutic effects of leukapheresis are due to the removal of factors capable of inhibiting normal hematopoiesis. This factor(s) is present in the cells that were removed by leuka-

pheresis. The exact nature of this factor(s) or the cells that produce this factor(s) remains to be identified. (Author abstract) (11 Refs)

40. USE OF CALF THYMOSIN IN TREATING ACUTE LEUKEMIA COMPLICATED WITH INFECTION.

DeptInternal Medicine
Tongren Hosp., Beijing, People's Republic of China
Zhonghua Neike Zazhi; 20(7):436-437 1981

Treatment of serious bacterial infections complicating acute leukemia is described for 12 cases. Thymosin fraction 5 (THF5) was extracted from the thymus gland of a 2-3-day-old male calf. After receiving THF5 (1-5 mg, sc, 1x daily, total dose 10-66 mg), six patients recovered, showing negative bacterial tests and normal or greatly improved T cell immune functions compared with patients who showed partial responses; one patient did not respond. (no Refs) (In CHI)

41. GRANULOMATOUS INFECTIONS COMPLICATING HAIRY CELL LEUKEMIA.

Rice L, Shenkenberg T, Lynch EC, Wheeler TM
Mail Station 902, 6565 Fannin, Houston, TX, 77030
Cancer; 49(9):1924-1928 1982

Of 14 patients with hairy cell leukemia (HCL), 4 developed opportunistic granulomatous infections: blastomycosis, coccidioidomycosis and two Mycobacterium kansasii. The former two pathogens have not been reported with HCL, while M kansasii infections appear to be common. While most reviews stress susceptibility to pyogenic bacteria and the predisposing role of iatrogenic factors, three of our patients were infected prior to any therapy. Thus, disease-related factors predispose to these granulomatous infections. Granulocytopenia and monocytopenia were present; the latter was not often corrected by splenectomy. There was impaired granuloma formation, with all infectious lesions appearing histologically as focal microabscesses containing few macrophages. Awareness of the frequency of opportunistic intracellular infections with early consideration of invasive diagnostic procedures to establish specific etiologic diagnosis may greatly prolong survival for many HCL patients. (Author abstract) (24 Refs)

42. APPLICATION OF CENTRAL VENOUS ACCESS AND INTRAVENOUS HYPERALIMENTATION TO THE MANAGEMENT OF PATIENTS WITH HEMATOLOGICAL MALIGNANCY.

Ohtake S, Yamamura M, Odaka K, Teshima H, Shiobara S, Kobayashi S, Matsue K, Ishino C, Yoshida T, Funada H, Nakamura S, Hattori KI, Harada M
Third Dept. Internal Medicine, Kanazawa Univ., Kanazawa, Japan
Rinsho Ketsueki; 22(11):1720-1728 1981

Intravenous hyperalimentation (IVH) using central venous access (CVA) was evaluated by applying 33 central venous catheters to 26 patients with hematological diseases (11 acute leukemias, 1 chronic myelogenous leukemia in blast crisis, 2 leukemic lymphosarcomatoses, and 3 malignant lymphoma). Ten cases had decreased platelet counts. The catheters were left in place for a median of 26 days (3-78 days) and were used for administration of iv drugs, fluids, blood components, as well as for the collection of blood. Two cases experienced easily managed site bleeding. No site infections occurred; septicemia was seen in five cases (15.2%). Those with poor oral intake of food showed no significant change in nutritional parameters before and after the application of IVH. These results suggest that CVA and IVH are useful in patient care, cause little discomfort, and may extend survival in selected patients. (24 Refs) (In JPN)

CASE REPORTS

43. NEUTROPHILIC ECCRINE HIDRADENITIS. A DISTINCTIVE TYPE OF NEUTROPHILIC DERMATOSIS ASSOCIATED WITH MYELOGENOUS LEUKEMIA AND CHEMOTHERAPY.

Harrist TJ, Fine JD, Berman RS, Murphy GF, Mihm MC
Warren 5, Dermatopathology Unit, Massachusetts General Hosp., Boston, MA, 02114
Arch Dermatol; 118(4):263-266 1982

On two occasions, erythematous edematous plaques developed on the left side of the neck and the left shoulder of a man undergoing induction chemotherapy for acute myelogenous leukemia. The lesions resolved after several days in both instances. Histologically, numerous neutrophils surrounded and focally infiltrated the eccrine secretory coils, in which epithelial necrosis was observed. The 'fixed' nature of the plaques and temporal relationship to chemotherapy suggest that the lesions represent an unusual reaction to chemotherapeutic agents. It is possible that this unique clinicopathologic picture represents a neutrophilic dermatosis associated with leukemia. (Author abstract) (22 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

44. RISK FACTORS IN THE ETIOLOGY OF LEUKEMIA.

Popovic K, Pejin D, Stefanovic N, Belic A, Djokic M, Uzurov V, Mihajlovic M, Popovic S, Spasojevic J
Klinika za interne bolesti, Medicinski fakultet, Novi Sad, Yugoslavia
Med Pregl; 34(9/10):417-424 1981

Exogenous and endogenous risk factors in the etiology of leukemia were discussed. Of 125 patients with leukemia, 47 had the disease when the study was performed (21 acute leukemia and 26 chronic leukemia) and 78 were retrospective analyzed. Of the 21 patients (11 men, 10 women; 25-77 yr old) with acute leukemia, 4 of them were exposed to benzene, 1 to synthetic fertilizers, 1 to irradiation, and 5 had familial history of cancer. Patients Rh phenotype CeDee were 52.3% (37.54% found in the general population), and 61.9% were HLA phenotype A2 (48.6% found in general population). Of the 26 patients (9 men, 17 women; 20-90 yr old) with chronic leukemia, 1 of them received for prolonged amount of time phenylbutazone, 2 had familial history of cancer, and 2 belonged to families with leukemia. Of the 78 retrospective patients (33 men, 45 women; 10-90 yr old) with acute leukemia, 1 of them was exposed to benzene, 1 to pesticide, 1 to irradiation, 5 had familial history of cancer, and 8 suffered viral infections shortly before. Differentiation of blood groups in all the patients was similar to the general population. (30 Refs) (In SCR)

45. FOUR CASES OF FAMILIAL CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA INCLUDING THREE CASES IN A SIBSHIP.

Tsunematsu Y, Koide R, Sasaki M, Utsumi J
Div. Hematology and Oncology, Natl. Children's Hosp., Tokyo, Japan
Rinsho Ketsueki; 22(12):1938-1947 1981

Four cases of familial childhood acute lymphocytic leukemia (ALL), including three cases in siblings, were studied. The fourth patient was a half cousin of the other three. The two families have had no contacts, and no specific environmental factors were noted. All four were in the same generation, and there were no marriages between the members of the family. Both families descended from a female who had two spouses, and the female's siblings all died within 8 yr of age. All siblings of the father of the three ALL cases also died in young ages, and one of them was suspected of having died of ALL. Two patients were examined by electron microscopy for C-type particles; none were found, nor were other inclusion bodies found. No reverse transcriptase was found in all patients. Pedigree analysis suggests that ALL cases were likely a result of a genetic mechanism with a dominant inheritance for genetic susceptibility. Immunogenetic examination revealed that the surviving patients and the obligate carriers had the same HLA haplotype, AW19 BW40. Chromosome analysis showed no chromosomal abnormality, but G-banding of skin fibroblast cells revealed chromosomal rearrangement in the patients and the obligate carriers. These two findings in cytogenetic and immunogenetic studies may be important as possible phenotypic markers for prediction of predisposition to leukemia. (35 Refs) (In JPN)

SELECTED PRE-CLINICAL STUDIES

46. SPECIFICITY STUDIES OF CYTOLYTIC T LYMPHOCYTES DIRECTED AGAINST MURINE LEUKEMIA VIRUS-INDUCED TUMORS. ANALYSIS BY MONOCLONAL CYTOLYTIC T LYMPHOCYTES.

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J Exp Med; 155(4):1050-1062 1982

Specificities of cloned cytolytic T lymphocytes (CTL) were investigated for the analysis of CTL populations generated against murine leukemia viruses (MuLV) in H-2 congenic BALB/c (H-2d) and BALB.B (H-2b) mice. CTL elicited by immunization with syngeneic Friend or Gross MuLV-induced tumors in these mice were studied. Optimal conditions for proliferation and long-term culture of MuLV-specific CTL were determined. Ninety-two lymphocyte clones were assayed independently on a panel of 51Cr-labeled tumor target cells. Clones were then distributed into different groups according to their specificities. Most of the CTL clones (52-64%) attacked the tumor cell against which they were initially primed and not any of the other tumor cells assayed. Other clones were specific for the priming MuLV-induced antigen in apparent association with an H-2 public specificity shared between H-2b and H-2d antigens (5-16%); were specific for tumor cells induced by Gross, Rauscher, Friend, and Moloney MuLV and were H-2 restricted (6 clones); was H-2b restricted and recognized only RBL-5 and HFL/b tumor cells of the Friend, Moloney, or Rauscher family (1 clone); showed a total lack of target specificity (21 clones); or lacked detectable cytotoxic activity (2 clones). Thus, the highly heterogeneous constitution of CTL populations generated against MuLV-induced tumors in BALB/c and BALB.B mice was demonstrated. (40 Refs)

47. AUGMENTATION OF THE ANTI-TUMOR THERAPEUTIC EFFICACY OF LONG-TERM CULTURED T LYMPHOCYTES BY IN VIVO ADMINISTRATION OF PURIFIED INTERLEUKIN 2.

Cheever MA, Greenberg PD, Fefer A, Gillis S
Div. Oncology, RK-25, BB1015 Health Sciences, Univ. Washington, Seattle, WA, 98195
J Exp Med; 155(4):968-980 1982

C57BL/6 mice bearing disseminated FBL-3 (a transplanted ascitic Friend's virus-induced leukemia) were treated with cyclophosphamide (CY: 180 mg/kg) and long-term cultured T lymphocytes (CTL) plus purified interleukin 2 (IL-2: 80 units/day). The long-term cultured T lymphocytes were highly cytotoxic to FBL-3, but not to an antigenically distinct C57BL tumor, EL-4(G-). CTL continued to proliferate in vitro and expand in number when repeatedly exposed to IL-2 in vitro; however, when cultured without IL-2, less than 10% remained viable at 72 hr. Gamma-irradiation reduced the number of viable cells to less than 5% at 72 hr, even in the presence of IL-2. When IL-2 was administered in vivo to mice with FBL-3 tumors, no detectable antitumor effect was observed, even with CY. Therapy on day 5 after tumor inoculation with CY plus CTL (5 x 10(6)) prolonged survival of mice but produced no cures. Treatment with CY plus CTL plus IL-2 on days 5-9 cured 11/16 mice. Thus, as an adjunct to CY, CTL were effective in tumor therapy, and their efficacy was significantly augmented by inoculation of exogenous IL-2. The in vivo efficacy of exogenous IL-2 in adoptive chemoimmunotherapy required that the effector cell be capable of proliferating in the host. While noncultured immune cells were effective in antitumor therapy, their efficacy was not augmented by exogenous IL-2. It is suggested that IL-2 promotes in vivo growth and/or survival of adoptively transferred cells. (41 Refs)

48. CHARACTERIZATION, TOXICITY AND THERAPEUTIC EFFICACY OF ADRIAMYCIN ENCAPSULATED IN LIPOSOMES.

Olson F, Mayhew E, Maslow D, Rustum Y, Szoka F
(c/o Mayhew) Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Eur J Cancer Clin Oncol; 18(2):167-176 1982

The inherent toxicities of drug-free liposomes were compared. Positively charged liposomes were more toxic in vitro (chick heart cells) and in vivo (5-fold reduction in LD50 in mice) than neutral or negatively charged liposomes. Based on these findings, adriamycin was encapsulated in negatively charged liposomes (PG: PC: Chol-1:4:5), sequentially extruded through polycarbonate membranes (to 0.2 um pore size) and purified by exhaustive dialysis. This preparation had a mean vesicle diameter of 0.24 um and was stable in serum (24 hr drug retention of 85%). As compared with free drug, liposome-encapsulated adriamycin was less toxic in vitro to chick heart cells. In mice, adriamycin displayed short- (4-14 day) and long- (45-70 day) term toxicity. Encapsulating adriamycin increased both short- (20-50 mg/kg) and long- (10-15 mg/kg to 25-30 mg/kg) term LD50 levels. As compared with free drug, administering encapsulated adriamycin in vivo reduced the incidence of cardiac histopathologic lesions at 20 and 40 mg/kg. Compared in vivo, plasma levels of liposome-encapsulated adriamycin were 2/3-fold higher than free drug up to 24 hr post drug administration. Cardiac uptake of adriamycin was re-

duced two-fold (conc x time value for 48 hr) following encapsulated drug administration. Encapsulating adriamycin in liposomes did not alter its therapeutic effect against L1210 leukemic cells in vivo. (Author abstract) (22 Refs)

REVIEWS

49. CYTOGENETICS OF PRELEUKEMIA.

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Cancer Genet Cytogenet; 5(3):265-278 1982

A summary is presented of the major cytogenetic findings in various hematopoietic disorders that carry an increased risk for leukemia, with emphasis on the more recent results with banding techniques. Groups of disorders discussed include cytopenic disorders (dysmyelopoietic syndromes, DS) (DS with specific chromosome changes, cytogenetic evolution and progression to leukemia, cytopenic preleukemia in patients previously treated for malignant disease, prognostic value of chromosome studies in cytopenic preleukemia); myeloproliferative disorders (MD) (prognostic value of chromosome studies in MD); and preleukemic disorders of childhood (clinical value of chromosome studies in childhood preleukemia). Biological significance of chromosome changes in preleukemia is considered. Some evidence suggests that chromosome studies may be of prognostic value in DS; patients with abnormalities show decreased survival time and are at increased risk for progression to ANLL (acute non-lymphocytic leukemia). Karyotypic findings in the preleukemias suggest that the various clinical disorders are a group of related diseases derived from an altered hemic stem cell. (61 Refs)

50. SUBACUTE AND CHRONIC MYELOMONOCYTIC LEUKEMIA.

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Clinique Haematologique Hotel Dieu, 1 Place du Parvis Notre Dame, 75181 Paris, Cedex 04, France

Haematol Blood Transfus; 27:157-165 1981

Development, prognosis, and treatment of subacute and chronic myelomonocytic leukemia (SMML and CMML, respectively) are discussed. Diagnosis is based on blood monocytosis greater than 10(9)/liter with immature and atypical circulating monocytes. Specific nosological and diagnostic difficulties are discussed. The incidence of SMML and CMML is undetermined. SMML is characterized by less than 30% blast cells and a progressive course leading to overt acute leukemia and/or death within 1 yr of diagnosis. CMML is characterized by a much longer survival than SMML (median of 40 mo vs 6 mo). Clinical and hematological differences between the two diseases were found with respect to sex ratio, duration of disease prior to diagnosis, Hb, circulating blasts, and bone marrow blasts; however, these were not sufficient to define a clear prognosis. Other biological aspects of SMML and CMML were examined. CMML was characterized by moderately increased serum levels of lysozyme with normal urinary levels in most cases, while SMML may have high serum and urinary levels of lysozyme. Increases in serum transcobalamin I and II were observed in some patients with CMML and SMML, but further studies must be performed. Of seven cases of CMML, normal or high numbers of colony-forming units (CFU)-GM was observed in five and a decrease or no CFU-GM activity was observed in two. All three cases of SMML had decreased numbers of colonies. The leukemic nature of SMML and CMML is discussed. Treatment of patients with SMML should include chemotherapy such as that used for other acute leukemias. Chemotherapy should be avoided in CMML except for cases with progressive myeloproliferation. (29 Refs)

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Diagnosis, Treatment

SERIES CT03 No. 82/10

OCTOBER, 1982

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DIAGNOSIS

1. PROGNOSTIC FACTORS OF SUBACUTE AND CHRONIC MYELOMONOCYTIC LEUKEMIA.

Zittoun R, Cailiou M, Kouzan S
Service d'Hematologie, Hotel Dieu, Place du Parvis Notre-Dame, F 75181 Paris Cedex 04, France
Ann Med Interne (Paris); 133(2):80-83 1982

The clinical, hematological, biological and prognostic features of myelomonocytic leukemias were studied in 11 patients with subacute myelomonocytic leukemia (SMML) and in 20 patients with chronic myelomonocytic leukemia (CMML). The men-to-women ratio was 2.33 in CMML and 0.83 in SMML; the median age was 63 yr for SMML patients and and 68 yr for CMML patients. Anemia, hyperleukocytosis, monocytosis, the number of circulating granulocytes and blast cells, and bone marrow blast count were found to be higher in SMML than in CMML, with significant differences for Hb, circulating and bone marrow blasts. High urinary lysozyme output, decrease in granulo-monocytic colonies after bone marrow culture on semi-solid media were further arguments in favor of the subacute type. This variety, which evolves into acute myelomonocytic leukemia in nearly 50% of all cases, appears con-

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sequently to be the first step of an acute leukemia, or represents a very close aspect. CMML is characterized by a steady course, (even still showing a 30% blast transformation) with a median survival of 3.3 yr, and with a notable percentage of untreated patients surviving several yr beyond this median survival. (13 Refs) (In FRE)

2. 'PROLYMPHOCYTOID' CELLS IN CHRONIC LYMPHOCYTIC LEUKAEMIA AND THEIR PROGNOSTIC SIGNIFICANCE.

Economopoulos T, Fotopoulos S, Hatzioannou J, Gardikas C
(c/o Gardikas) Medical Unit, Evangelismos Hosp., Athens 140, Greece
Scand J Haematol; 28(3):238-242 1982

The morphology of lymphocytes in blood and bone marrow smears from 103 patients with chronic lymphocytic leukemia (CLL) was studied. Special attention was paid to the finding of immature cells with the morphological features of prolymphocytes (prolymphocytoid cells - PLC). Subsequently the prognostic significance of these cells was examined. It was found that in 85 cases no PLC were found (Group I); in 8 cases the percentage was less than or equal to 10% (Group II) and in 10 cases the PLC were greater than 10% (Group III). The cases with PLC, especially in group III, fell in advanced stages of the disease (III-IV) and presented with increased lymphocytosis. In 8 patients of group III, who were followed till death, the disease became refractory to any treatment and the survival was short. We suggest that 'prolymphocytoid' transformation is a bad prognostic sign in CLL. (Author abstract) (8 Refs)

3. ACUTE MYELOID LEUKEMIA WITH HAND-MIRROR CELLS.

Haider YS, Phillips TM, Schumacher HR
(c/o Schumacher) Div. Hematopathology, Dept. Lab. Medicine, Natl. Naval Medical Center, Bethesda, MD, 20014
Arch Pathol Lab Med; 106(6):271-274 1982

A retrospective analysis of 37 cases of acute myeloid leukemia (AML) seen during 5 yr was undertaken to evaluate the presence in the bone marrow of hand-mirror cells (HMCs). Three cases with greater than 5% HMC were investigated by light and electron microscopy, cytochemistry, levels of terminal-deoxynucleotidyl-transferase, study of histologic aspects of bone marrow clot and biopsy specimens, and bone marrow immune complexes for numerous viruses. The findings supported the myeloid nature of the HMC; however, immune complexes associated with the baboon endogenous virus were absent, a finding that has been observed in all cases of acute lymphoblastic leukemia (ALL) with HMCs so studied. In light of this finding, it was suggested that HMCs are produced in ALL and AML by different mechanisms. In addition, the patients with AML-HMC did not survive longer than those without HMCs in the bone marrow. Further studies in larger groups are needed to clarify the phenomenon of HMC formation in AML and its relation to survival. (Author abstract) (18 Refs)

4. ENRICHMENT OF CELL POPULATIONS CONTAINING TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY BY FREE FLOW ELECTROPHORESIS.

Sarin PS, Virmani M, Gallo RC
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Int J Cancer; 29(5):501-506 1982

Terminal deoxynucleotidyl transferase (TdT) is an enzyme that has been utilized as a biochemical marker for following certain leukemia patients during treatment and remission. The potential usefulness of this enzyme in predicting the onset of relapse before any morphological indications has been demonstrated in chronic myelogenous leukemia patients in blast phase of the disease. In order to be able to detect low levels of TdT activity, especially during remission phase, we have used the technique of free flow electrophoresis to enrich cell populations containing TdT. With this technique we have achieved up to 20-fold enrichment of TdT-positive cell populations from normal human bone marrow, cells from patients with acute lymphoblastic leukemia and chronic myelogenous leukemia in blast phase of the disease. TdT positive cells were not detected in patients with acute myelogenous leukemia and B cell lines. This technique should prove to be useful in early detection of relapse in patients in remission and for enrichment of cell populations containing other biochemical markers. (Author abstract) (22 Refs)

5. III - EVALUATION OF PROGNOSTIC VALUE OF PLASMA PHOSPHOHEXOSE ISOMERASE LEVELS IN LEUKEMIA PATIENTS DURING THERAPY.

Seshadri KN, Talageri VR, Advani SH
Cancer Res. Inst., Tata Memorial Hosp., Parel, Bombay 400 012, India
Indian J Cancer; 19(1):28-34 1982

Plasma phosphohexose isomerase (PHI) levels were studied in 20 normal subjects and 93 patients with leukemia (34 chronic myeloid leukemia (CML), 16 acute myeloid leukemia, 22 acute lymphatic leukemia (ALL), 13 chronic lymphatic leukemia (CLL), and 8 acute monomyeloid leukemia (AMML)). PHI levels were about 3x higher in the leukemic patients than in the normal subjects. PHI levels were elevated in 87-91% of CML, ALL, and CLL patients and in 70-75% of AML and CLL cases. In 11/14 patients studied during therapy, plasma PHI activity was correlated with WBC count. Increases in the plasma PHI levels were clearly associated with increases in the activities in WBC in CML, AML and AMML cases, although this relationship was not linear. About 14 cases have been studied to evaluate the usefulness of PHI as a marker during therapy; four case histories are presented. Before PHI may be used as a prognostic marker, serial measurements of the enzyme should be made at different stages of the disease and for longer periods of time. (12 Refs)

6. A NOVEL ALKALINE PHOSPHATASE ISOZYME IN 4 PATIENTS WITH ACUTE NON-LYMPHOCYTIC LEUKEMIA: ITS NATURE, ORIGIN AND CLINICAL SIGNIFICANCE.

Leroux-Roels GG, Van Hove WZ, Wieme RJ
Dept. Internal Medicine, Univ. Hosp., Gent, Belgium
Oncodev Biol Med; 3(1):31-47 1982

A novel alkaline phosphatase (AP) isozyme has been observed in the serum of four patients suffering from acute non-lymphocytic leukemia (ANLL). It resembled the AP of liver/bone origin in most physico-chemical characteristics, but particular electrophoretic characteristics in agar and starch gel and a distinct molecular wt gave this novel AP isozyme its unique character. Its leukemic origin has been demonstrated by isolation from peripheral blood and bone marrow blasts. The appearance of the novel AP isozyme in the patients' sera appeared to be an ominous sign as, in all four, it shortly preceded death. In two patients it may have contributed to the observed resistance towards thioguanine therapy. (Author abstract) (31 Refs)

7. NONSPECIFIC ESTERASE CYTOCHEMISTRY IN ACUTE MYELOBLASTIC LEUKEMIA: ALPHA-NAPHTHYL ACETATE VERSUS ALPHA-NAPHTHYL BUTYRATE (MEETING ABSTRACT)

Cerezo L, Head DR
Department of Pathology, Brooke Army Medical Center, Fort Sam Houston, TX
Am J Clin Pathol; 77(2):248 1982

Nonspecific esterase activity (NSE) is a recognized property of monocytes and is used widely as a marker to identify myeloblastic leukemias (AML) of monocytic type. However, stains employing different substrates exist and cytochemical results from different laboratories may not be comparable. We studied the NSE of AML cases registered on a Southwest Oncology Group study performing both alpha-naphthyl acetate esterase (ANA; pararosanilin; pH 6.1) and alpha-napthyl butyrate esterase (ANB; Fast Red PDC; pH 7.4) stains on bone marrow smears. All diagnoses of AML were made using the criteria of the FAB classification and NSE in the primitive cells was required for a diagnosis of M4 or M5. Preliminary findings include the evaluation of 34 cases initially classified as M1 or M2 on the basis of Sudan black B positivity and alpha-naphhthyl butyrate esterase negativity. Five of 34 (14.7%) were ANA positive, indicating a true diagnosis of myelomonocytic leukemia (M4). This NSE also was inhibited by NaFl in two cases in which incubation with NaFl was performed also. These cases of M4 would have been diagnosed as M1 (three cases) and M2 (two cases) if only ANB had been examined. In two of the five cases M4 had been suspected on the basis of blast morphology. (no Refs)

8. BIOPTERIN LEVEL IN PERIPHERAL BLOOD CELLS AS A MARKER FOR HEMOPOIETIC CELL PROLIFERATION DURING LEUKEMIA AND POLYCYTHEMIA VERA.

Ziegler I, Fink M, Wilmanns W
Institut fur Toxikologie und Biochemie, Abteilung Zellchemie, Gesellschaft fur Strahlen- und Umweltforschung mbH, Arcisstr. 16, D-8000 Munchen 2, W. Germany
Blut; 44(4):231-240 1982

Biopterin (BP) levels in whole blood and distribution of BP between various fractions of blood were studied in patients with leukemia and polycythemia vera (PV) using the Crithidia assay. Increased BP levels were more characteristic for myelocytic leukemias (ML) and PV than for lymphocytic leukemias. An indication of concomitant increases in BP level and in blast number was obtained by following a few patients at short intervals during blast crisis. Changes in blast numbers and BP levels were closely synchronized. Normal distributions of BP among various fractions of blood from eight healthy donors and amounts of BP in cellular fractions of blood, BP concentration/unit of cellular protein, and BP percentage distribution during blast crisis of chronic ML (CML), PV, and lymphocytic leukemias are presented. In both clonal hemopathies (CML and PV), the amount of BP was increased in the RBC fraction and also in the buffy coat. In CML the increase in the WBC is more accentuated, whereas in PV the increase is in the red cell BP. A reduction in the amount of RBC BP and a reduced percentage contribution of RBC BP are characteristic for both chronic and acute lymphocytic leukemias (ALL). Especially during ALL, BP contribution to the total of cell BP increased up to a 10-fold value of the normal lymphocyte contribution. In all cases of effective therapy, BP values tended to normalize and even reached normal levels; high erythrocytic and granulocytic levels during blast crisis dropped whereas pathologically low levels in the RBC fraction increased to fairly normal levels, including all cases of lymphocytic leukemias. (17 Refs)

9. A COLLABORATIVE STUDY OF THE RELATIONSHIP OF THE MORPHOLOGICAL TYPE OF ACUTE NONLYMPHOCYTIC LEUKEMIA WITH PATIENT AGE AND KARYOTYPE.

Rowley JD, Alimena G, Garson OM, Hagemeijer A, Mitelman F, Prigogina EL
Box 420, 950 East 59th St., Chicago, IL, 60637
Blood; 59(5):1013-1022 1982

Data on the chromosome analysis of leukemic cells from consecutive patients with nonlymphocytic leukemia from six independent laboratories in the United States, Europe, and Australia were combined. The karyotypic pattern determined with banding was correlated with the patient's age and the morphological type of leukemia according to the FAB classification. Of the 503 patients in the combined study, 260 had acute myeloblastic leukemia (AML, M1 and M2), 142 had acute myelomonocytic leukemia (AMMoL, M4), 43 had acute monocytic leukemia (AMoL, M5), 30 had erythroleukemia (EL, M6), and 28 had acute promyelocytic leukemia (APL, M3). The percentage of patients with an abnormal karyotype was higher in EL (63%) and AML (59%) than in AMMoL (40%) and AMoL (42%). Loss of no. 5 and/or no. 7 occurred in 30% of all EL patients, in 19% of all AML patients, and in only 7% of AMMoL, in 5% of AMol, and in 4% of APL patients. These observations are significant because patients with ANLL secondary to aggressive therapy for a primary malignant disease tend to have AML or EL, and the majority have-5 and/or-7. These same morphological types of leukemia and the same abnormalities,-5 and/or-7, are also increased in patients with ANLL de novo who have a history of occupational exposure to potentially mutagenic substances. In the future, the type of leukemia and the particular karyotypic pattern may be useful in identifying a subset of patients with ANLL de novo whose leukemia may be mutagen-induced. (35 Refs)

10. PROGNOSTIC SIGNIFICANCE OF POSTTRANSFUSION HEPATITIS AND CHROMOSOMAL ABNORMALITIES IN ADULT ACUTE NONLYMPHOCYTIC LEUKEMIA.

Wong KK, Golomb HM, Rowley J, Baker AL, Testa J, Vardiman J (c/o Golomb) Dept. Medicine, Univ. Chicago Hosp. and Clinics, Box 420, 950 East 56th St., Chicago, IL, 60637
Cancer Genet Cytogenet; 5(4):281-292 1982

In a retrospective analysis, we studied the effects of posttransfusion hepatitis (non-A, non-B) and chromosomal abnormalities upon the overall survival times of adult patients with acute nonlymphocytic leukemia (ANLL). Seventy-two patients treated at the University of Chicago from 970 to 981 were evaluable. The complete remission (CR) rate for the entire group of patients was 33%, and the median survival was 246 days. Twenty-eight patients (39%) developed hepatitis, and 42 (61%) did not. The CR rate of the patients with hepatitis was 54%, and the median survival of this group was 615 days. In comparison, the CR rate for those who did not develop hepatitis was 20%, and their median survival was 136 days (p less than 0.0001). The groups were comparable in terms of race, sex, initial hematologic parameters, chromosomal abnormalities, dates of treatment, chemotherapy treatment programs, and French-American-British (FAB) subtype, but the median age of the patients who did not develop hepatitis was higher than that of the others. Patients who had normal karyotypes and who developed hepatitis had the best overall prognosis (median survival of 738 days). Patients with abnormal karyotypes who failed to develop hepatitis had the shortest survival times (median, 124 days). The group of patients who had the longest

survival (median, 1,130 days) included those over 40 yr old, with posttransfusion hepatitis, and with normal karyotypes. The development of posttransfusion hepatitis and the presence of chromosomal abnormalities appear to be important, but opposite, indicators of overall prognosis for patients with ANLL. (Author abstract) (19 Refs)

11. CYTOGENETIC AND HEMATOLOGIC FINDINGS IN ACUTE MYELOGENOUS LEUKEMIA, M2 ACCORDING TO THE FAB CLASSIFICATION.

Oshimura M, Ohyashiki K, Mori M, Terada H, Takaku F
Dept. Cytogenetics, Medical Res. Inst., Tokyo Medical and Dental Univ., Yushima 1-5-45, Bunkyo-ku, Tokyo 113, Japan
Gan; 73(2):212-216 1982

Chromosome banding studies on leukemic cells from 12 patients with acute myelogenous leukemia (AML), M2 according to the FAB classification, were performed. In eight cases, chromsome abnormalities were observed; among these eight, six were found to exhibit a common chromosome abnormality, ie, t(8;21)(q22;q22). The present findings strongly support the view that AML with t(8;21)(q22;q22) represents a definite subgroup within the general category of AML; this translocation has not been observed in more than 100 cases of leukemias other than AML M2. When the chromosome findings were collated with the hematologic and clinical data, it was found that the cases with t(8;21)(q22;q22) were not distinguishable from those with karyotypes other than the translocation in M2, in terms of hematologic and clinical findings. (Author abstract) (14 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

12. AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN LYMPHOID MALIGNANCIES. LACK OF CORRELATION WITH DISEASE ACTIVITY OR CLINICAL REMISSION.

Quesada JR, Reuben JM, Scouros MA, Murphy SG
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, Anderson Hosp. and Tumor Inst., 6723 Bernter Ave., Houston, TX, 77030
Cancer Immunol Immunother; 12(3):231-239 1982

Status of the autologous mixed lymphocyte reaction (AMLR) was investigated in 30 patients with chronic lymphocytic leukemia (CLL) and the autologous reactivity was correlated with the extent of the disease by studying patients in different clinical stages. T lymphocytes from patients with CLL were highly enriched. The reactivity of T cells from patients with CLL in different clinical stages was compared with that of normal volunteers. The mean counts per minute (CPM) for patients in Stage I and Stage II was similar (1,969 +-317 and 1,789 +-537, respectively). Three patients in Stage III showed a lower mean CPM (894 +-149), but this was not significantly different from other stages. A marked difference in 3H-thymidine incorporation between patients with CLL and the control subjects was observed. The magnitude of the response to autologous non-T cells did not significantly differ between untreated patients and those who had received chemotherapy. Patients in Stage III showed the lowest response to phytohemagglutinin which may be partially related to the lower number of T cells in the responder population. Nine patients with CLL were studied while in clinical remission following cytotoxic chemotherapy. A markedly depressed AMLR was observed in all nine patients (mean 2,123 +-648 CPM) compared to normal subjects (mean 24,734 +-3,266 CPM). This reactivity did not differ significantly from that observed in patients with active disease as a group (mean 1,441 +-300; Stages I-III) or when compared with values for each clinical stage. The allogeneic reactivity of these cells when stimulated with irradiated non-T cells from normal subjects was preserved (22,545 +-7,781 CPM). The AMLR in six patients with malignant lymphoma in remission was subnormal (median 3,000 CPM). (43 Refs)

13. INFLUENCE OF MATURE AND IMMATURE MYELOID CELLS ON LYMPHOCYTE REACTIVITY IN CHRONIC MYELOCYTIC LEUKEMIA.

Ogier C, Sjogren AM, Reizenstien P
(c/o Reizenstein) Div. Hematology, Karolinska Hosp., S-104 01 Stockholm, Sweden
Cancer Immunol Immunother; 12(3):241-245 1982

In vitro mitogen-induced transformation of lymphocytes from 16 patients (24-78 yr old) with chronic myelocytic leukemia (CML) in different stages and that of normal lymphocytes after the addition of leukemic myeloid cells was studied. Lymphocytes from CML patients were significantly less markedly stimulated by phytohemagglutinin (PHA) and by Concanavalin A (ConA) than control lymphocytes. Heavy-density cells contained more than 95% polymorphonuclear granulocytes with a viability of more than 99%, both in CML patients and in normal controls. The light-density mononuclear cell fraction contained lymphocytes with less than 5% polymorphonuclear cells in controls, but up to 53% polymorphonuclear cells and up to 29% immature myeloid cells in patients. When the light-density mononuclear cells from CML patients were passed through nylon wool column, the percentage of polymorphonuclear cells fell to less than 10%. The rest were mononuclear cells with column-damaged morphology, probably immature myeloid cells. Normal lymphocytes stimulated with PHA in the presence of column-passed, light-density leukemic mononuclear cells reacted significantly less strongly than when they were stimulated in the presence of heavy-density CML cells, and numerically less than when they were stimulated in the presence of heavy-density normal cells. The more cells were added, the more inhibition of the PHA-induced transformation of normal lymphocytes was observed. Increasing amounts of leukemic cells resulted in a decreasing response to PHA. This effect appeared more pronounced for the light-density, immature, column-passed mononuclear cells than for the heavier, more mature granulocytes. (19 Refs)

14. MONOCLONAL ANTIBODY BA-1 DOES NOT BIND TO HEMATOPOIETIC PRECURSOR CELLS.

Jansen J, Ash RC, Zanjani ED, LeBien TW, Kersey JH
(c/o Kersey), Univ. Minnesota, Box 609 Mayo, 420 Delaware St. S.E., Minneapolis, MN, 55455
Blood; 59(5):1029-1035 1982

Monoclonal antibody BA-1 binds to B-lymphocytes, to cells from most cases of non-T acute lymphoblastic leukemia (ALL), and weakly to neutrophils. To determine whether BA-1 also reacts with hematopoietic progenitor cells (HPC), we studied the effect of removal of BA-1+ cells from human bone marrow on the proliferation in vitro of the trilineage precursor cell CFU-GEMM, and of the committed progenitor cells of granulopoiesis (CFU-C) and erythropoiesis (BFU-E/CFU-E). Complement-mediated cytotoxicity using BA-1 at concentrations far beyond those required to lyse BA-1+ bone marrow

cells and ALL cells did not result in inhibition of colony formation in any of the assays. A rosette separation method, using ox red blood cells coated with BA-1, resulted in enrichment of HPC in the BA-1-depleted interface, whereas very few HPC were found in the BA-1-enriched pellet. Both methods indicate that BA-1 does not bind to HPC, although binding of the antibody to the lymphohematopoietic stem cell cannot be excluded yet. The high cytotoxic capacity of the IgM antibody BA-1, and the lack of reactivity with HPC, make the antibody particularly suitable for use in autologous bone marrow transplantation for patients with ALL. (Author abstract) (26 Refs)

15. MURINE MONOCLONAL ANTIBODY THERAPY IN TWO PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Dillman RO, Shawler DL, Sobol RE, Collins HA, Beauregard JC, Wormsley SB, Royston I
Hematology/Oncology Section (111E), Univ. California, Veterans Admin. Hosp., 3350 La Jolla Village Drive, San Diego, CA, 92161
Blood; 59(5):1036-1045 1982

We infused the murine monoclonal antibody T101 into two patients with advanced refractory chronic lymphocytic leukemia (CLL) after confirming its reactivity with their CLL cells. One patient received doses of 1, 3, and 12 mg; the second patient received 10 mg. Antibody was delivered over 10-15 min. The major observations were: (1) T101 murine monoclonal antibody did bind to cells with T65 surface antigen and saturated these cells in vivo; (2) cells that bound T101 disappeared from the circulation by 2 hr after treatment, as evidenced by a marked drop in lymphocyte counts; (3) T101 serotherapy resulted in some intravascular cell injury associated with sequestration and probably destruction in the liver and lung; (4) free serum T101 was demonstrable, but disappeared by 2-4 hr after infusion; (5) rapid infusion of T101 did not induce significant modulation of T65; (6) rapid infusion of greater than 10 mg of T101 was associated with significant systemic reactions. Monoclonal antibodies may someday have an application in leukemia therapy, but additional experimental trials are clearly indicated. (Author abstract) (26 Refs)

CHEMOTHERAPY

16. TREATMENT OF PATIENTS WITH REFRACTORY MYELOGENOUS LEUKEMIA WITH BCOMM [1,3-BIS-CHLORO(2-CHLOROETHYL)-1-NITROSOUREA (BCNU), ONCOVIN (VINCRISTINE), CYCLOPHOSPHAMIDE, HIGH-DOSE METHOTREXATE, AND METHYL-GLYOXAL BIS-GUANYLHYDRAZONE (MGBG)].

Herman TS, Durie BG, Hutter JJ
Dept. Internal Medicine, Section Hematology/Oncology, Univ. Arkansas Medical Sciences, Little Rock, AR, 72206
Cancer Chemother Pharmacol; 8(1):73-75 1982

Ten patients (6 males, 4 females; 8-61 yr old, median age 22 yr) with myelogenous leukemia (9 acute, 1 chronic in blastic crisis) refractory to anthracyclines and cytosine arabinoside were treated with the BCOMM drug regimen [oncovin, 1.4 mg/square meter (m2) iv on day 1; methotrexate (MTX), 2.5 g/m2 iv bolus 30-60 min later on day 1; citrovorum factor, 10 mg/m2 iv every 6 hr for 12 doses or 100 mg/m2 every 3 hr for 32 doses begun 24 hr after MTX; carmustine (BCNU), 80 mg/m2 iv bolus 36 hr after MTX; cyclophosphamide (CY), 900 mg/m2 36 hr after MTX; and methyl-glyoxal bis-guanylhydrazone (MGBG), 300 mg/m2 iv over 1-2 hr approx 24 hr after BCNU and CY and repeated on days 4 and 5]. Complete remission (CR) was achieved in 5/10 patients, all of whom had relapsed from an initial CR. Two patients who were primarily resistant to these agents attained good partial responses and one entered CR after further treatment with 4-(9-acridinylamino)-methanesulfon-m-anisidide. In the five patients who entered CR, median time to bone marrow recovery was 25 days (range 21-40) after the start of therapy. Median duration of CR was 24 wk (range 8-38). Three patients received maintenance therapy. Median survival for patients who achieved CR was 40 wk and for those who did not, 10 wk. Two patients died of sepsis after treatment. One patient who achieved CR survived for 112 wk and another survived for 70 wk. Toxicities included nausea and vomiting (8 patients), stomatitis (5), and generalized erythematous cutaneous reaction (1). The BCOMM drug combination produced a higher proportion of CR of longer duration than seen with single agents. (15 Refs)

17. CLINICAL AND CELL KINETIC STUDIES OF THE EFFECTS OF THE EPIPODOPHYLLOTOXIN VP16-213 DURING THERAPY OF REFRACTORY ACUTE NONLYMPHOCYTIC LEUKEMIA.

Look AT, Dahl GV, Rivera G, Mauer AM
Div. Hematology-Oncology, St. Jude Children's Res. Hosp., 332 N. Lauderdale, P.O. Box 318, Memphis, TN, 38101
Cancer Chemother Pharmacol; 7(2/3):161-167 1982

The efficacy of two new drugs, VP16-213 and 5-azacytidine (5AZ), both effective single agents for therapy of refractory acute nonlymphocytic leukemia (ANLL), was tested in 24 patients (11 male, 13 female; 1-19 yr old), who had induction failure (5) or were in relapse (19). The treatment schedule was 200 mg VP16-213/square meter (m2) iv daily x 3 days followed by 300 mg 5AZ/m2 iv daily X 2 days. Until bone marrow hypoplasia was found by marrow aspiration, the schedule was repeated every 1-2 days. Nineteen of 24 patients had marrow hypoplasia and 11/24 achieved complete remission; of the latter 11, 5 remained in remission for 12-29 wk, demonstrating a highly effective drug combination. The effect of VP16-213 on leukemia blast proliferation was studied using patient serial bone marrow aspiration and DNA histogram analysis. G2 phase cell cycle arrest was found in leukemic blasts of all eight patients studied 4 and 24 hr after initial VP16-213 administration. DNA histogram analysis indicated a decrease in the number of cells in DNA synthesis after three daily doses of VP16-213. Such an occurrence is probably due to selective killing of cells in the S-phase by the drug compared to those in the G0/G1 phase. (18 Refs)

18. VM26 THERAPY IN CHILDREN WITH DRUG-REFRACTORY LYMPHOCYTIC LEUKEMIA.

Rivera G, Dahl GV, Murphy SB, Bowman WP, Aur RJ, Thomas, Avery L, Simone JV
St. Jude Children's Res. Hosp., 332 N. Lauderdale, P.O. Box 318, Memphis, TN, 38101
Cancer Chemother Pharmacol; 7(2/3):169-172 1982

The combination of VM26 and cytosine arabinoside (ara-C) was studied in Phase I and II trials in patients with drug refractory lymphocytic leukemias. A drug regimen consisting of five increasing dosages of VM26 combined with a constant ara-C dosage was used in treatment of 33 children with acute lymphoblastic leukemia (ALL) and multiple hematologic relapses; 10/33 patients achieved remission but an optimal dosage of VM26 in combination with ara-C was not established. Since

the effectiveness of VM26 is dosage-dependent, the drugs should be used at the maximally tolerated dosage. The effect of VM26 and ara-C was also studied in 26 children in second remission, which is generally short lived. Treatment with VM26 [165 mg/square meter(m2)] and ara-C (300 mg/m2) over 2 wk resulted in prolonged second remission (7 mo vs 3 mo in controls). Using a similar dosage schedule, a complete remission rate of 64% was found in 14 patients who were initial induction failures. A drug synergism study of VM26, prednisone and vincristine in 53 patients with refractory ALL showed 17 children attaining complete remission. These results suggest that clinical resistance to a drug may be overcome by adding an effective new drug with a different spectrum of antitumor activity. (18 Refs)

19. RESPONSE TO 5-AZACYTIDINE IN PATIENTS WITH REFRACTORY ACUTE NONLYMPHOCYTIC LEUKEMIA AND ASSOCIATION WITH CHROMOSOME FINDINGS.

Larson RA, Sweet DL, Golomb HM, Testa JR, Rowley JD
Box 420, 950 E. 59th St., Chicago, IL, 60637
Cancer; 49(11):2222-2225 1982

Fifteen patients with acute nonlymphocytic leukemia (ANLL) who either had a relapse after a previous complete remission (nine patients) or progressive disease after initial induction attempts with combination chemotherapy (six patients) were treated with 5-azacytidine. Five patients (33%) achieved a complete remission (CR); of these, three had a relapse and died 30, 35, and 38 wk after 5-azacytidine therapy was begun. Two patients are still alive at 39 and 138 wk. Chromosomes were analyzed at the time of diagnosis; ten patients had a normal karyotype and five had an abnormal karyotype. Three of the five CR patients had an abnormal karyotype initially. Two of these individuals had a translocation of chromosomal material from a No 8 chromosome to a No 21 chromosome, t(8;21); this particular translocation has been associated with a better prognosis than have other types of chromosomal abnormalities in patients with ANLL. Even when abnormal chromosomes are present, 5-azacytidine can induce complete remission in patients with previously treated ANLL. (Author abstract) (11 Refs)

20. 5-AZACYTIDINE IN REFRACTORY ACUTE LEUKEMIA.

Case DC
Div. Hematology and Oncology, Dept. Medicine, Maine Medical Center, Portland, ME, 04102
Oncology; 39(4):218-221 1982

Eleven patients (aged 23-75 yr) with refractory acute leukemia were treated at the Maine Medical Center with 5-Azacytidine, 150 mg/m2/day, by continuous infusion for 5 days every 2 wk. Prior therapy included anthracycline/cytosine arabinoside protocols. Of the eight patients with refractory de novo acute myelogenous leukemia, six achieved remission at an overall response rate of 75% (3 complete remission and 3 partial remission). An av of 1.67 courses was necessary to achieve a response. Remissions were not seen in blastic chronic myelogenous leukemia nor in acute leukemia secondary to cytotoxic drugs. Toxicity included myelosuppression, moderate nausea and vomiting, abnormal liver function tests, and neuromuscular symptoms. 5-Azacytidine by continuous infusion has significant activity in refractory acute myelogenous leukemia and should be considered for inclusion in primary remission induction therapy. (Author abstract) (20 Refs)

21. LYCURIM (NSC 122402) IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA.

Klener P
2nd Dept. Medicine, Div. Hematology, Charles Univ. Hosp., 128 08 Prague, Czechoslovakia
Neoplasma; 29(1):87-92 1982

Twenty five patients with aggressive form of chronic lymphocytic leukemia were treated with Lycurim, administered intravenously in a dose of 1 mg/kg every other day. In 19 patients objective response with average duration of 4 mo was achieved. The drug was effective even in cases who had become resistant to conventional therapy with chlorambucil or cyclophosphamide. Lycurim appears be useful alternative treatment modality of chronic lymphocytic leukemia. (Author abstract) (10 Refs)

22. GONADAL MORPHOLOGY IN PATIENTS RECEIVING CHEMOTHERAPY FOR LEUKEMIA. EVIDENCE FOR REPRODUCTIVE POTENTIAL AND AGAINST A TESTICULAR TUMOR SANCTUARY.

Kuhajda FP, Haupt HM, Moore GW, Hutchins GM
Dept. Pathology, Johns Hopkins Hosp., Baltimore, MD, 21205
Am J Med; 72(5):759-767 1982

To evaluate the possible reproductive potential in patients who receive chemotherapy for leukemia, we reviewed the gonadal histologic findings at autopsy in 183 treated leukemic patients and in 183 age- and sex-matched control subjects. The 103 male leukemic patients had significantly reduced spermatogenic activity and tubular fertility index and increased interstitial fibrosis as compared with control subjects (p less than 0.001). The 80 females had marked reduction of secondary follicles (p less than 0.001). These lesions showed no predilection for grouping by sexual maturity or by leukemia diagnosis. There was no correlation with the type of chemotherapy or time since last dose of any antileukemic agent. Despite these extensive pathologic changes, there was histologic evidence of residual reproductive potential - a tubular fertility index greater than zero in 65% of males and intact primary follicles in 81% of premenopausal females. Testicular leukemia was present in 25% of males; all of the patients with testicular leukemia had additional foci of leukemia in other organs. The study shows histologic evidence of possible reproductive potential in treated leukemic patients of both sexes and does not support the concept of the testis as a tumor sanctuary in leukemia. (Author abstract) (29 Refs)

MULTIMODAL THERAPY

23. TREATMENT OF ACUTE MYELOID LEUKAEMIA IN CHILDREN.

Paton CM, Ekert H, Waters KD, Matthews RN, Toogood RG
(c/o Ekert) Dept. Clinical Hematology and Oncology, Royal Children's Hosp., Flemington Road, Parkville, Victoria 3052, Australia
Aust NZ J Med; 12(2):143-146 1982

Complete remission was achieved in 11 of 22 children with acute myeloid leukemia using at least two courses of a 24 hr infusion of cytosine arabinoside (Ara-C) 10 mg/kg, followed by push injections of daunorubicin (DNR) 45 mg/m2, and adriamycin (ADR) 45 mg/m2. Consolidation therapy consisted of three courses of Ara-C and 6-thioguanine (Tg) and one course of cyclophosphamide (CPA) and ADR. Central ner-

vous system prophylaxis with intrathecal Ara-C was given in all patients and cranial irradiation in five. Maintenance therapy consisted of 5 day courses of Ara-C and Tg given 4 weekly with immunotherapy (BCG vaccine and subcutaneous leukemic cells) between courses. Median length of first complete remission was 99+ wk, and median survival of all patients was 44 wk. Median survival of remitters was 195+ wk and non-remitters, 28 wk. Two patients developed central nervous system disease, one at presentation and the other 46 wk from presentation. Five patients have ceased therapy and remain in remission from 32 to 142 wk after ceasing treatment. (Author abstract) (16 Refs)

SUPPORTIVE CARE

24. EXPERIENCE WITH A COOPERATIVE BONE MARROW TRANSPLANTATION PROGRAM IN STOCKHOLM.

Ringden O, Lonnqvist B, Lundgren G, Gahrton G, Groth CG, Moller E, Baryd I, Johansson B, Pihlstedt P, Gullbring B
Div. Transplantation Surgery, Dept. Surgery, Huddinge Hosp., S-141 86 Huddinge, Sweden
Transplantation; 33(5):500-504 1982

Twenty-seven patients (age range from 1 to 55 yr) were included in a cooperative bone marrow transplantation program in Stockholm. Of eight patients with severe aplastic anemia (SAA), two died following graft rejection and six (75%) are alive between 3 mo and 4 1/2 yr after transplantation. Two patients with end stage leukemia died of septicemia and bleeding shortly after transplantation. Thirteen of 17 patients (76%) with acute leukemia in their first or second remission are alive 1 to 16 mo after transplantation. Death was caused by septicemia in two patients, interstitial Candida pneumonitis in one and gastrointestinal bleeding in association with graft-vs-host disease in one. Among the leukemic patients all deaths occurred in subjects over 17 yr of age and all 10 children are alive. No relapse has yet been seen. Successful bone marrow transplantations were carried out utilizing ordinary hospital resources only. This justifies the practice of performing transplantations in subjects with SAA and acute leukemia in remission even outside specially equipped and designed bone marrow transplantation units. (Author abstract) (25 Refs)

25. INCIDENCE, PROGNOSIS AND PREVENTION OF SEPTICEMIAS IN PATIENTS UNDER TREATMENT FOR ACUTE LEUKEMIA.

Gastant JA, Marsninchi D, Liegey DB, Lejeune C, Novakovitch G, Sebahoun G, Meyer G, Carcassonne Y
Clinique de maladies du sang, Laboratoire de bacteriologie, Institut J. Paoli-I. Calmettes, 232, boulevard de Sainte-Marguerite, F 13273 Marseille Cedex 2, France
Nouv Presse Med; 11(8):579-582 1982

Septicemias are frequent and severe in patients with acute leukemia under aplastic treatment. The present study concerns 69 such patients: 29 with acute lymphoblastic leukemia (ALL), and 40 with acute non-lymphoblastic leukemia (ANLL). All were treated in single rooms in the same hospital and in similar conditions. The overall incidence of septicemia was 62%; it was 60% in patients with recently diagnosed ALL and 68% during relapses. More than 34% of ALL patients and 82.5% of ANLL patients had one or several episodes of septicemia. Among the 74 pathogens isolated 50% were Gram-positive organisms, 45% Gram-negative organisms and 5% Candida spp. The first episodes of septicemias were predominantly caused by Gram-positive spp (61%) and the subsequent ones by Gram-negative spp (60%). The primary infection could only be diagnosed in 19% of the cases and was most frequently located in the digestive tract or perineal region. The most common focal complications were lung infections (18 cases), skin infections (12 cases) and septic shock (15 cases). Seventy-four percent of the patients survived with prompt and potent antibiotic therapy. Death occurred in 26% and was clearly related to the following factors: chemotherapy of relapsed leukemia and/or blastic aplasia and/or successive episodes of septicemia. The incidence and severity of septicemias in leukemic patients will only be reduced by improved prophylactic measures against infection and by less pronounced and shorter chemotherapy-induced granulocytopenia. (Author abstract) (15 Refs) (In FRE)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

26. A RETROVIRUS ASSOCIATED WITH HUMAN ADULT T CELL LEUKEMIA: IN VITRO ACTIVATION.

Hinuma Y, Gotoh Y, Sugamura K, Nagata K, Goto T, Nakai M, Kamada N, Matsumoto T, Kinoshita K
Inst. Viral Res., Kyoto Univ., Shogoin Kawahara-machi, Sakyo-ku, Kyoto 606, Japan
Gan; 73(2):341-344 1982

Presence of adult T cell leukemia antigen (ATLA) was studied in the mononuclear cell fractions of peripheral blood derived from 11 patients (9 men, 2 women; 48-83 yr old) with adult T cell leukemia (ATL), from a 54-yr-old man with mycosis fungoides (MF), and from 8 healthy adults (6 men, 2 women; 21-44 yr old). The mononuclear cell fractions were cultured in the presence and/or absence of interleukin-2 (IL-2) or T cell growth factor. Some of the fractions were also examined with electron microscopy for virus particles. ATLA positive cells were not detected in any of the cell preparations examined prior to culturing. However, ATLA-bearing cells were observed in the cultures from 6/11 ATL patients and 1/2 ATLA antibody-positive healthy subjects. No ATLA-bearing cells were detected in cultures of one patient with MF and six ATLA antibody-negative healthy subjects. High percentages of ATLA positive cells were found 2-3 days after starting cultures without IL-2; the ATLA were located in the cytoplasm of rather small leukemic cells and were often aggregated. The ATLA-bearing cells in cultures supplemented with IL-2 for a greater than 2 wk were large and often multinuclear with blastoid morphology. Presence of Type C virus particles was observed with electron microscopy in ATL-derived cultures with a high percentage of ATLA positive cells. The results showed that (1) peripheral blood cells of many patients with ATL contain sufficient information for ATLA or ATL virus (ATLV) formation in a repressed form, and suggest that (2) ATLA is associated with ATLV and (3) ATLV is present not only in ATL patients but also in anti-ATLA positive healthy individuals. (6 Refs)

27. ASYMPTOMATIC TYPE C VIRUS CARRIERS IN THE FAMILY OF AN ADULT T CELL LEUKEMIA PATIENT.

Miyoshi I, Taguchi H, Fujishita M, Niiya K, Kitagawa T, Ohtsuki Y, Akagi T
Dept. Medicine, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan
Gan; 73(2):339-340 1982

Serologic and virologic studies were performed in 14 members of the family of a 49-yr-old male patient with adult T cell leukemia (ATL). The patient and family lived in Kochi, an area where the incidence of ATL appears to be relatively high. ATL antigens (ATLA) and Type C virus particles were detected in short-term cultures of peripheral lymphocytes from 4/5 family members who were ATLA antibody positive. The five ATLA antibody positive family members were all asymptomatic and hematologically normal except for one member, in whom a persistent leukocytosis with several percent abnormal lymphocytes had been observed for two yr. It was not yet determined whether vertical or horizontal infection was involved in the virus transmission in this family. (5 Refs)

28. THE ASSOCIATION OF HAIRY CELL LEUKEMIA WITH UNUSUAL IMMUNOLOGIC DISORDERS.

Dorsey JK, Ponick GD
Dept. Internal Medicine, Univ. Iowa Hosp. and Clinics, Iowa City, IA, 52242
Arch Intern Med; 142(5):902-903 1982

Hairy cell leukemia is a rare disease, probably of B-lymphocyte origin, that has been reported to rarely occur with polyarteritis nodosa. The records of 31 patients with hairy cell leukemia were reviewed for an association with other disorders of the immune system; such an association was found more often than previously suspected. Four cases are discussed - one with hepatitis B surface antigen-positive polyarteritis nodosa and another with an IgA (kappa) monoclonal gammopathy and amyloidosis of the kidney, liver, and small bowel. The other two patients had cutaneous vasculitis, one of which was a rare form of leukocytoclastic angiitis - erythema elevatum diutinum. Because the number of patients in this study is small, it is impossible to say whether the association of hairy cell leukemia with any of these immunologic disorders adversely affects survival. (Author abstract) (13 Refs)

SELECTED PRE-CLINICAL STUDIES

29. EXPRESSION OF HLA ANTIGENS ON LEUKEMIA CELLS.

Mayer S, Tongio MM, Falkenrodt A, Pfeiffer B, Bergerat JP
Institut d'Hematologie, Centre de Transfusion Sanguine, 10, rue Spielmann, 67085 Strasbourg Cedex, France
J Immunogenet; 9(2):111-120 1982

HLA antigens of 10 leukemic cell lines were investigated using an absorption method and the results were compared with those of normal lymphocytes. Cell lines from five patients with acute myeloblastic leukemia, one with acute lymphocytic leukemia, two with blastic lymphomas, one with acute myelomonocytic leukemia, and one with chronic granulocytic leukemia in an acute lymphoblastic crisis were used. The number of pathological cells exceeded 80% in seven patients and 60% in three. A detailed leukocyte count is presented. Anti-B5, anti-B7, and anti-B12 sera were absorbed on the healthy lymphocytes and the 10 leukemia cell lines and the residual cytotoxicity is illustrated. For anti-A1 + B8 and anti-A2 sera, only leukemia cells were used for absorption. Leukemia cells absorbed anti-HLA antibodies as effectively as healthy lymphocytes when the cells carried the antigen corresponding to the serum specificity. The curves obtained with leukemia cells were comparable to those of healthy cells. Leukemia cells were also capable of absorbing antibodies when the cells were not carriers of the antigen corresponding to the antibody's specificity. Only a few types of healthy lymphocytes were capable of weak absorption of anti-HLA sera. In most cases, 500 leukemic cells were sufficient to absorb anti-HLA sera and the absorption usually increased with the number of cells used. This 'non-specific' absorption was poorer than that noted with cells carrying the antigen corresponding to the antibody. In most cases, non-specific absorptions could not be explained by cross-reactions. (11 Refs)

REVIEWS

30. CHRONIC MYELOCYTIC LEUKEMIA. TREATMENT AND BIOLOGY.

Preisler HD, Higby DJ
Dept. Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY
NY State J Med; 82(5):703-710 1982

Chronic myelocytic leukemia, although a relatively rare hematologic malignancy, is an intriguing disorder. Although the course of the generally benign chronic phase lasts for 2.5 to 3.5 years there is in fact significant variability in patient survival; 20% of patients expire within 1.5 years of diagnosis while another 20% are still in the chronic phase of the disease 5 years after diagnosis. Ultimately the majority of patients enter a universally fatal phase resembling acute leukemia. The presence of the Philadelphia chromosome can be used as a marker for evaluating and following the disease through its chronic and acute phases. Cell surface markers may provide additional diagnostic information. Therapy during the chronic phase is fairly standard with busulfan being almost universally used. Given the poor responsiveness of blast crisis and other transformation events to chemotherapy, attention has been turned to hematopoietic transplantation for the treatment of endo-stage disease. For theoretical reasons transplantation prior to the clinical onset of blast crisis may be preferable. (Author abstract) (49 Refs)

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DIAGNOSIS

1. ACUTE LEUKEMIAS IN ELDERLY PATIENTS.

Grunewald K, Abbrederis K, Mittermaier P, Huber H
Institut fur Medizinische Chemie und Biochemie, Fritz-Pregel-Str. 3, A-6020 Innsbruck, Austria
Blut; 44(5):289-296 1982

Correlation between the subtypes of leukemia and age was investigated in 186 patients (15-90 yr old) with acute leukemia. Diagnosis was established according to cytomorphological and cytochemical classification. Sex distribution and age groups are presented. Seventy patients (37.6%) were greater than 60 yr old, and 53 (28.5%) greater than 65 yr old. Majority of 65-yr-old patients had acute myelogenous leukemia (AML) which was diagnosed in approx 42% of all patients. Acute monocytic, promyelocytic, and cytochemically undifferentiated leukemia (CUL) were frequent in the older age groups; 37.5%, 32.1%, and 33.3%, respectively. Fifty percent (FP) survival rate for greater than 60-yr-old patients was 2.5 mo. FP survival rate of 15-30-yr-old and 30-60-yr-old patients was 6 mo. No significant difference was observed between the survival rate of AML and acute nonmyelogenous leukemia (ANML). One- and 2-yr survival for ANML was 35% and 24%, respectively, and for

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AML only 19% and 9%, respectively. Significant difference was observed in the survival curves at 5%. FP survival rate for all patients (11% of patients greater than 60 yr old) was 20.2 mo and for CUL patients (40% of patients greater than 60 yr old) 2 mo. Survival for 78 patients with AML grouped according to age is presented. Early deaths were correlated with age; no long time survivors were observed among patients greater than 57 yr old. (31 Refs) (In GER)

2. STAGING OF CHRONIC LYMPHOCYTIC LEUKEMIA.

Baccarani M, Cavo M, Gobbi M, Lauria F, Tura S

(c/o Cavo) Inst. Hematology 'Lorenzo e Ariosto Seragnoli', S. Orsola's Univ. Hosp., via Massarenti 9, 40138, Bologna, Italy

Blood; 59(6):1191-1196 1982

One-hundred and eighty-eight patients with chronic lymphocytic leukemia were analyzed for prognosis based on Rai's staging system. It was found that Stages I and II were not homogeneous as to prognosis. Stage II patients presenting with isolated splenomegaly had a long survival and were pooled with Stage 0 patients (low risk group, 30% of cases, relative death rate 0.24, median survival greater than 10 yr). Stages I and II patients with a lymphocyte count higher than 40 x 10(9)/liter had a short survival and were pooled with Stages III and IV patients (high risk group, 39% of cases, relative death rate 1.91, median survival 3.3 yr). Stages I and II patients with a lymphocyte count lower than 40 x 10(9)/liter made up an intermediate or standard risk group (31% of cases, relative death rate 1.00, median survival 6.2 yr). This modified staging system applied successfully to both old and young patients (more and less than 60 yr old, respectively). (Author abstract) (26 Refs)

3. ASSESSMENT OF MARROW TREPHINE IN RELATION TO STAGING IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Bartl R, Frisch B, Burkhardt R, Hoffmann-Fezer G, Demmler K, Sund M

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Br J Haematol; 51(1):1-15 1982

The prognostic value of the Rai clinical staging system and of a series of bone marrow features was examined in 167 untreated patients with CLL. the patients fell into three prognostic groups: those with limited disease, Rai Stages 0 and I, median survival 107 mo; those with intermediate disease, Rai Stage II, median survival 44 mo; and those with extensive disease, Rai Stages III and IV, median survival 27 mo. Two types of infiltration patterns, diffuse and nodular, were found in bone marrow, and these were associated with significantly different median survival times: 34 and 115 mo respectively. It is suggested that diffuse and nodular patterns in the bone marrow relate to the rapidity of progress of the disease rather than to different stages in CLL. The data suggest that a simplified clinical staging system together with an histological classification reflects both the extent as well as the rate of progression of CLL. The course of CLL may be monitored by sequential bone marrow biopsies to assess changes in the proliferation pattern, in the proliferative cell system and in the tumor mass, which give early warning of shifts in the rate of progression and therefore in the prognosis of the disease. (Author abstract) (35 Refs)

4. FREQUENCY OF EARLY DEATH IN CHILDREN WITH ACUTE LEUKEMIA PRESENTING WITH HYPERLEUKOCYTOSIS.

Wald BR, Heisel MA, Ortega JA

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Cancer; 50(1):150-153 1982

The relationship of hyperleukocytosis, early death, and intracerebral hemorrhage was determined in 547 pediatric patients with acute leukemia. Hyperleukocytosis occurred in 7.3% of patients with acute leukemia. The early mortality rate was significantly increased in hyperleukocytic patients when compared to the nonhyperleukocytic group. Hyperleukocytic patients with ANLL had a significantly greater risk of early death than nonhyperleukocytic patients with ANLL. The difference in the incidence of early death between hyperleukocytic and nonhyperleukocytic patients with ALL/AUL was not statistically significant. In the hyperleukocytic patients intracerebral hemorrhage was the universal cause of early death but this entity did not occur in any of the nonhyperleukocytic patients. There was no correlation of intracerebral hemorrhage to thrombocytopenia or coagulation abnormalities. Autopsies confirmed intracerebral hemorrhage and leukostasis with leukemic infiltration of the brain tissue. (Author abstract) (21 Refs)

5. VARIATIONS IN THE ACTIVITY OF NUCLEOLAR ORGANIZERS IN DIFFERENT TISSUES, DEMONSTRATED BY SILVER STAINING OF HUMAN NORMAL AND LEUKEMIC CELLS.

Reeves BR, Casey G, Harris H

Dept. Cytogenetics and Immunogenetics, Inst. Cancer Res., Royal Marsden Hosp., Fulham Road, London SW3 6JJ, England

Cancer Genet Cytogenet; 6(3):223-230 1982

A simple silver-staining technique that demonstrates those nucleolar organizing regions of metaphase chromosomes which are transcriptionally active during the preceding interphase (AgNORs) has been applied to cells obtained from the bone marrow and mitogen-stimulated peripheral blood lymphocyte cultures of hematologically normal individuals and patients with various forms of leukemia. In the majority of bone marrow cells from the normal controls and many of the patients, the numbers of cells with detectable AgNORs, and the staining intensities in those cells which were AG+, were markedly reduced compared with the levels found in blood lymphocytes. The numbers of cells having satellite associations and the numbers of chromosomes participating in these associations also generally reflected the proportions of AgNORs present. When patterns of bone marrow silver staining were compared between patients with leukemia, distinct differences were found which could be correlated with cytology. It is suggested that different cell types have characteristic AgNOR staining profiles, reflecting specific regulation of ribosomal RNA synthesis in particular cell lineages. AgNOR staining may indicate, therefore, the predominant cell types that divide in the bone marrows of patients with different forms of leukemia. (Author abstract) (23 Refs)

6. ULTRASTRUCTURAL CHARACTERIZATION OF DE NOVO AND SECONDARY LEUKEMIAS.

Butler AE, Vardiman JW, Golomb HM
(c/o Golomb) Dept. Medicine, Section Hematology/Oncology, Univ. Chicago, Box 420, 950 East 59th St., Chicago, IL, 60637
Virchows Arch [Cell Pathol]; 39(3):239-257 1982

Cells from 95 patients with acute leukemia were studied by cytochemistry, light microscopy, and transmission electron microscopy (TEM), and were classified according to the French-American-British (FAB) guidelines. This group included 63 patients with acute nonlymphocytic leukemia (ANLL) de novo, 18 with acute lymphocytic leukemia (ALL), and 14 with ANLL as a second malignancy. In addition, 13 cases of chronic myelocytic leukemia in blast crisis were studied. Ultrastructural examination resulted in reclassification of six cases of ANLL de novo; two of these were reclassified from M2 (myeloblastic leukemia with maturation) to M3 variant (microgranular variant of hypergranular promyelocytic leukemia). The classification of the cases of CML in blast crisis was identical by light microscopy and TEM. In one case of myeloblastic crisis, however, basophilic granules were demonstrated by TEM but were not appreciated by light microscopy. Classification of the cases of secondary leukemia was possible by light microscopy and cytochemistry in all 14 cases, but was often difficult since the cytochemical reactions were usually less intense than in de novo ANLL. This was particularly true in those cases classified as M1, and in such cases, TEM was required to confirm the diagnosis. (Author abstract) (24 Refs)

7. RELATIONSHIP OF PRETREATMENT LYMPHOBLAST PROLIFERATIVE ACTIVITY AND PROGNOSIS IN 97 CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Dow LW, Chang LJ, Tsiatis AA, Melvin SL, Bowman WP
St. Jude Children's Res. Hosp., P.O. Box 318, 332 North Lauderdale, Memphis, TN, 38101
Blood; 59(6):1197-1202 1982

We have analyzed the pretreatment 3H-thymidine labeling indices in blood and marrow blast cells from 97 children with acute lymphoblastic leukemia (ALL) and circulating blasts. The median marrow labeling index (LI) was 6.2% (range 0.8%-32.7%) and the median blood LI, 3.2% (range 0.3%-20%). Blood LI was significantly correlated with leukocyte count and rosette-forming (E+) lymphoblasts but not with central nervous system leukemia or thymic mass at diagnosis. Marrow LI was related to E+ blasts only. In children with E+ leukemia, both blood and marrow LIs were significantly higher than values for other ALL subtypes (p less than 0.01) excluding undifferentiated ALL, which was characterized by an increased blood LI. Eighteen patients had a blood LI that either equaled or exceeded the marrow LI; apart from age, the clinical features, blast phenotypes, and treatment responses of this group were similar to those of patients with blood LI less than marrow LI. Among 51 patients assessed for treatment response, the estimated median length of remission was significantly shorter for those with a blood LI greater than 4% ($p = 0.002$) or a marrow LI greater than 6% ($p = 0.011$). By Cox-regression analysis, the pretreatment proliferative activity of blood and marrow blasts, unlike other initial features studied, added significant prognostic information to leukocyte count in these patients with circulating blasts. The findings provide a cogent explanation for the differential clinical responsiveness of commonly recognized ALL subclasses. (Author abstract) (30 Refs)

8. NUCLEAR TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN LEUKAEMIC INFILTRATES OF TESTICULAR TISSUE.

Thomas JA, Janossy G, Eden OB, Bollum FJ
Dept. Immunology, Royal Free Hosp. Sch. Medicine, London, England
Br J Cancer; 45(5):709-717 1982

Early detection of testicular leukemia and the identification of residual leukemic cells in treated patients are important aims in the management of males with acute lymphoblastic leukemia (ALL). In most cases of ALL (greater than 95%) the blast cells express terminal deoxynucleotidyl transferase (TdT), a nuclear enzyme. We have therefore standardized the immuno-fluorescence and -peroxidase techniques (using anti-TdT antibodies) for identifying TdT+ cells in the normal thymus, as well as in samples of testis with heavy leukemic infiltrates (positive controls). TdT+ cells can be identified in formalin (but not in Bouin's or Carnoy's) fixed paraffin-embedded tissues, and the preservation of morphological details is excellent. The method is nevertheless difficult to standardize and also requires the use of deoxyribonuclease (DNase) for the digestion of sections. However, in frozen tissue sections, stronger staining of TdT+ cells was found, even without DNase treatment. Good morphology was preserved when cut sections were fixed immediately in the cryostat. In the second part of the study 15 samples from treated boys were analyzed to see whether the technique is suitable to identify residual minimal leukemic infiltrates. In five patients scanty disseminated TdT+ cells were detected, and in two patients small clumps of TdT+ cells were seen. The results indicate that the immunohistological identification of TdT+ ALL blasts may be the method of choice. (Author abstract) (14 Refs)

9. ALPHA-NAPHTHYL ACETATE ESTERASE ZYMOGRAM IN LEUKEMIC CELLS.

Usui T, Konishi H, Sawada H, Uchino H, Ohtsuki H
First Div. Internal Medicine, Kyoto Univ., Kyoto, Japan
Nippon Ketsueki Gakkai Zasshi; 45(1):91-96 1982

The zymogram of nonspecific esterase was examined by polyacrylamide gel electrophoresis in 28 patients with various leukemias. None to eight cathodal and two to three anodal bands, in comparison with bromphenol blue dye front, were detected. Anodal bands were observed in all types of leukemic cells. A few weak cathodal bands were shown in acute myelogenous leukemia (AML) cells, while four to seven strong cathodal bands were seen in other non-lymphoid leukemic cells. In lymphoid leukemic cells, the most cathodal band, which was completely sodium fluoride (NaF) resistant, was usually visible. In blastic crisis of chronic myelogenous leukemia (CML-BC), zymograms in terminal deoxynucleotidyl transferase (TdT) negative and positive cells were similar to those of acute promyelocytic leukemia (APL) cells and lymphoid leukemic cells, respectively. However, no cell-type specific bands were detected in the present study. (Author abstract) (13 Refs)

10. PROPERTIES OF LYMPHOCYTE 5'NUCLEOTIDASE IN NORMAL SUBJECTS AND PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Conklyn MJ, Silber R
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Leuk Res; 6(2):203-210 1982

Heterogeneity of 5'nucleotidase (5NT) was studied in normal and in chronic lymphocytic leukemia (CLL) lymphocytes.

5NT reaction velocity was proportional to the incubation time for up to 2 hr to the amount of protein over a concentration ranging from 1-52 ug/assay. The effect of various substrates on the reaction rate of plasma membrane 5NT obtained from normal and CLL lymphocytes is shown. When lymphocyte membranes from 5NT negative CLL donors were assayed, no activity with any of the substrates was observed even when the incubation period was extended to 5 hr. Inosine monophosphate was compared to AMP as a substrate using nonhomogenized cells and subcellular fractions from normal and CLL lymphocytes. AMP was consistently a better substrate for the ecto-5NT. A very wide but reproducible range of Km values, from 19-210 uM was found with nonhomogenized lymphocytes while a much lower Km value with a narrow range was observed with the plasma membranes. An unexpected relationship was observed between Km values and the specific activity of the lymphocytes. Lymphocyte preparations which had higher specific activity also had higher Km values for AMP. Dialysis of lymphocyte homogenates overnight against Tris-dithiothreitol buffer resulted in a marked decrease in Pi levels but had no effect on the Km. The addition of Pi to a final concentration of 1 milliM did not affect the Km. Studies of heat stability showed that the enzyme in CLL and in normal lymphocytes was relatively stable at 54 C. (20 Refs)

11. SIALYLTRANSFERASE ACTIVITY IN LEUKEMIA.

Sasaki R, Takaku F, Lin YL, Boilum FJ
Dept. Hematology, Jichi Medical Sch., 311-1 Yakushiji Minamikawachi-Machi, Kawaschi-Gun, Tochigi 329-04, Japan
Leuk Res; 6(2):197-202 1982

Assayed sialyltransferase activity (STA) in blasts from various types of leukemia patients was compared with the level of activity in mature lymphocytes or granulocytes. STA in blasts from acute lymphoblastic leukemia (ALL) patients was markedly lower (1.68 +-1.23 picomole; pmol/mg protein) than those (6.18 +-2.22 pmol/mg protein) of lymphocytes from the peripheral blood of normal volunteers. Also, in blasts from terminal transferase (TdT)-positive chronic myeloid leukemia (CML) patients in blasts crisis, a low level of the enzyme activity compatible to those of ALL patients was observed. STA was significantly increased in blasts (1.21 +-0.38 pmol/mg protein) from patients with acute non-lymphoblastic leukemia including acute myeloblastic leukemia, acute myelomonocytic leukemia, and acute promyelocytic leukemia, compared to the level of mature granulocytes (0.53 +-0.32 pmol/mg protein). However, only a slight difference was observed between the level of STA in the granulocytes from CML patients in chronic phases and in the granulocytes from normal volunteers. In TdT-negative CML in blast crisis, STA (2.11 +-0.88 pmol/mg protein) was significantly higher than those of mature granulocytes from normal controls, whereas no significant difference of the enzyme activity was noted between the blasts from TdT-positive CML in blast crisis and from ALL. (27 Refs)

12. UNUSUAL BIOCHEMICAL PATTERN OF SERUM ADENOSINE DEAMINASE ACTIVITY IN ACUTE LYMPHOBLASTIC LEUKAEMIA.

Gakis C, Piras MA, Romani G
Clinica delle Malattie infettive dell'Universita di Sassari, via Manno, 54-07100 Sassari, Italy
Haematologica (Pavia); 67(2):199-206 1982

Twenty-nine patients with leukemia (11 acute lymphoblastic leukemia, ALL; 6 chronic lymphocytic leukemia; 1 acute myeloid leukemia; 8 chronic myeloid leukemia; 2 subacute monocytic leukemia; and 1 blastic leukemia of uncertain classification, BL) were tested for adenosine deaminase activity (ADA) in serum. Most patients were diagnosed for the first time and were receiving no therapy. Normal sera were obtained from 17 healthy volunteers. The ADA for relative substrate specificity revealed two different enzymatic patterns within the ALL group. Treated patients had a deaminase ratio of 0.30 and 0.37 respectively, consistent with the 'serum type' enzyme present in other disease conditions previously studied. Untreated patients displayed a major activity on 2'deoxyadenosine with a deaminase ratio ranging from 0.51-0.72 consistent with the 'tissue type' enzyme. Individual values of deaminase ratio are shown indicating how the ratio enables differential diagnosis, whereas the assay on ADA alone does not. A curve with an optimum pH from 6.0-7.0 characterized the serum enzyme in viral hepatitis and 'null' cell ALL in remission, whereas both 'undifferentiated' and 'T-cell' ALL in acute phase displayed a curve with optimal pH between 7.0-7.7 overlapping that of lymphocyte lysate. Moreover, the substrate-activity curves confirmed in two cases a tissue type Km much lower than in 'null' cell ALL in remission. In other groups, the only patient showing similar biochemical properties in the serum enzyme activity had BL. (13 Refs)

13. ARYL SULFATASE A IN ACUTE NONLYMPHOCYTIC LEUKEMIA.

Pillai MV, James GW, King ME, Fox FW, Choi SC
Medical Coll. Virginia, Virginia Commonwealth Univ., PO Box 445, Richmond, VA, 23298
Am J Hematol; 12(3):305-307 1982

To ascertain whether estimation of urinary aryl sulfatase A (ASA) is a reliable noninvasive technique for monitoring disease activity in adult acute nonlymphocytic leukemia, we studied the excretion pattern of this enzyme during active disease, partial remission, and complete remission in 10 patients and compared the results with those of 10 healthy volunteers. There was no significant difference in enzyme excretion between complete remission cases and the control group. Patients with partial remission and active disease had significantly different urinary enzyme levels from each other and from the control and complete remission groups. Estimation of urinary ASA is a useful noninvasive method of monitoring disease activity in adult acute nonlymphocytic leukemia. (Author abstract) (4 Refs)

14. A COMPARATIVE STUDY OF THE EFFECTIVENESS OF DIFFERENT MITOGENS FOR KARYOTYPIC ANALYSIS IN CHRONIC B CELL LEUKEMIA.

Katz RL, Cork A, Cox I, Murphy SG, Trujillo JM
Dept. Cytopathology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, 6723 Bertner, Houston, TX, 77030
Leuk Res; 6(2):183-195 1982

Karyotypic abnormalities were studied in nine patients (8 males, 1 female, 38-76 yr old, mean age 63 yr) with chronic lymphatic leukemia using a combination of T and/or B cell mitogens. Clinical and hematological data at the time of sampling are presented. Eight out of nine patients demonstrated the presence of the mu heavy chain either alone, or as noted in two patients, together with delta or gamma chain on greater than 60% of the cells counted. The DNA synthetic capacity of the heterogenous population of neoplastic B lymphocytes and residual lymphocytes was assessed by the uptake of tritiated thymidine following incubation with different mitogens. Phytohemagglutinin (PHA) proved to be an effective inducer following incubation at 3-and 6-day intervals. Chromosome damage (CD)

was noted to occur with pokeweed mitogen, lipopolysaccharide from Escherichia coli, and PHA with no evidence of an increased predilection for any one mitogen to reveal more damage than another. CD took the form of chromatid breaks, isobreaks, acentric fragments, deletions, and translocations. In addition, dicentric, ring, triradial, and minute chromsomes were observed on occasion. The results of HLA typing in the patients revealed a high incidence of cells (56%) positive for the HLA-A33 antigen. The frequency of this antigen as compared with that found in a normal donor panel matched for racial and ethnic origin was significant. The HLA-A24 antigen was observed in 33% of the patients, compared with an expected frequency of 18% for this population. (22 Refs)

15. FURTHER CHARACTERIZATION OF ACUTE MYELOGENOUS LEUKEMIA WITH T(8; 21) CHROMOSOME TRANSLOCATION.

Sakurai M, Kaneko Y, Abe R
Saitama Cancer Center, 818 Komuro, Ina, Saitama 362, Japan
Cancer Genet Cytogenet; 6(2):143-152 1982

All seven patients with t(8; 21)(q22; q22) and one with a del(8)(q22) had a diagnosis of acute myelogenous leukemia (AML)-M2 type. Similar morphologies of leukemic cells with a t(8q-; 21q+) or with an 8q-, as well as the association of the latter with loss of a sex chromosome, indicated that the translocation or deletion of chromosome No 8 at q22 may be essential to the phenotypic expression and loss of a sex chromosome in cells with the translocation. Seven patients (1 in Group I, 4 in Group II, and 2 in Group III) were in remission and four relapsed. All patients at relapse had acquired additional autosomal abnormalities, which were related to changes in cell morphology and relapse. (Author abstract) (29 Refs)

16. CORRELATION OF KARYOTYPE WITH CLINICAL FEATURES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Kaneko Y, Rowley JD, Variakojis D, Chilcote RR, Cheek I, Sakurai M
(c/o Rowley) Dept. Medicine, Univ. Chicago, Box 420, 950 East 59th St., Chicago, IL, 60637
Cancer Res; 42(7):2918-2929 1982

We studied the clinical and karyotypic features of 50 patients with acute lymphoblastic leukemia, including 33 American and 17 Japanese patients, at two institutions. Clonal chromosome abnormalities were found in 39 of the 50 patients (78%) at diagnosis. Eleven patients had diploidy (N patients). Among the 39 aneuploid patients, 17 had pseudodiploidy (A1 patients), eight had hyperdiploidy with 47 to 49 chromosomes (A2 patients), nine had hyperdiploidy with 50 to 59 chromosomes (A3 patients), and five had other chromosome abnormalities. Of 14 patients whose chromosomes were also studied at relapse, eight had karyotypic progression, five had abnormalities identical or similar to those observed at diagnosis, and one had a change of karyotype from diploidy to aneuploidy. The median age and the median white blood cell count (WBC) of A3 patients were lower than those of any other group of patients, and all A3 patients had non-T-cell non-B-cell markers. The median age and the median WBC of A1 patients were higher than those of any other group of patients, although one-third of the patients had WBC below 20 x 10(3)/ul, and they often had leukemic cells of T-cell or B-cell lineage. The A2 patients were relatively old and tended to have higher WBC. The N patients were relatively young and tended to have low WBC, although these tendencies were not as marked as those in A3 patients. The A3 patients had longer survival times than the A1 ($p = 0.003$) or A2 ($p = 0.002$) patients. Also, N patients had longer survival times than A1 ($p = 0.03$) or A2 ($p = 0.05$) patients. The difference in survival times between A3 and N patients was not significant. Our study demonstrated that the karyotype is correlated with survival and with other recognized prognostic factors. However, in some A1 and A2 patients, the karyotype was a more reliable factor in indicating a poor prognosis than was the WBC or age. (Author abstract) (46 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

17. T-CELL SUBPOPULATIONS IDENTIFIED BY MONOCLONAL ANTIBODIES AFTER HUMAN MARROW TRANSPLANTATION. I. HELPER-INDUCER AND CYTOTOXIC-SUPPRESSOR SUBSETS.

Atkinson K, Hansen JA, Storb R, Goehle S, Goldstein G, Thomas ED
Dept. Haematology, St. Vincent's Hosp., Darlinghurst, Sydney, NSW 2010, Australia
Blood; 59(6):1292-1298 1982

Peripheral blood helper-inducer and cytotoxic-suppressor T-cell subpopulations in patients receiving marrow transplants for the treatment of acute leukemia or severe apiastic anemia were quantitated on the fluorescence-activated cell sorter (FACS) using the monoclonal antibodies OKT4 and OKT8, respectively. The relative (percent) and absolute number of OKT4+ cells were severely and persistently depleted for up to 2.7 yr posttransplant. In contrast, the percent and absolute number of OKT8+ cells began to recover within the first 60 days of transplant and subsequently remained at normal or high levels for periods of up to 7.3 yr. There was no significant difference in percent or absolute numbers of OKT8+ cells for patients with or without acute graft-vs-host disease (GVHD). The reversal of the normal OKT4:OKT8 ratio (2:1) occurred regardless of whether the recipient was given an allogeneic, syngeneic, or autologous transplant and regardless of whether or not acute or chronic GVHD developed. The reversed ratio was due in the first 3 mo posttransplant to low numbers of OKT4+ cells and later to a combination of low numbers of OKT4+ and high numbers of OKT8+ cells. Normalization and then an increase in the number of OKT8+ cells correlated with increasing time posttransplant and not with resolution of acute GVHD. (Author abstract) (21 Refs)

18. UTILITY OF MONOCLONAL ANTIBODIES IN THE IMMUNOLOGIC PHENOTYPING OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Yu AL, Royston I, Leung KL, Kung FR, Hartman GA, Lightsey AL, Vangrove T, Sobol RE
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Hybridoma; 1(2):91-98 1982

Two monoclonal antibodies were used in conjunction with conventional lymphocyte markers to characterize acute lymphoblastic leukemia (ALL) in 34 children and 11 adults. Monoclonal antibody T101 detects a 65,000 mol wt cell surface antigen (T65) found on all T-cells in the peripheral blood and lymph node, T-cell lines, and thymocytes; the second antibody detects a monomorphic determinant on the Ia-like antigen, which is a bimolecular complex of 27,000 and 35,000 mol wt. Four distinct phenotypes were evident in the childhood ALL

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patients; the most common of these was observed in 22 patients. The marker profiles of the 11 adult patients exhibited the four phenotypes found in the childhood cases, and one additional phenotype. The most common phenotype, found in 6/11 patients, was the same as the most common phenotype in the childhood group. Reactivity with monoclonal anti-Ia and anti-T65 antibodies appears to define two distinct clinical subgroups of childhood ALL. The more common group was Ia+T65-and was characterized by an equal male:female distribution; younger age, lower leukocyte count, and lower incidence of organ involvement at presentation; and longer disease-free survival than Ia-T65+ patients. The less common Ia-T65+ group was associated with male predominance, anterior mediastinal mass, high leukocyte count, organ involvement, and early treatment failure. Anti-Ia and T101 reactivity are apparently mutually exclusive in ALL, since no Ia+T65+ patients were identified. (24 Refs)

19. A NEW ACUTE LEUKEMIA-ASSOCIATED BLAST CELL ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY.

Billing R, Lucero K, Shi BJ, Terasaki PI
Tissue Typing Lab., Dept. Surgery, Univ. California Los Angeles, 1000 Veteran Ave., Room 15-22, Los Angeles, CA, 90024
Blood; 59(6):1203-1206 1982

A monoclonal mouse antibody has been raised to the common acute lymphoblastic leukemia (cALL) cell line Reh. It is a cytotoxic antibody of the IgG2a subclass that reacts with leukemia cells from the following patients: 69% non-B non-T ALL, 50% T-ALL, 18% acute myeloblastic leukemia (AML), and 66% chronic myeloid leukemia (CML) blast crisis lymphoid cells. Other types of leukemia and all normal blood cells tested were negative, including T and B lymphocytes, granulocytes, monocytes, erythrocytes, and spleen cells. The detected antigen appears to be a type of blast cell antigen because it is also present on phytohemagglutinin (PHA) blast cells, myeloblast from normal bone marrow cells (by CFU-C), and all lymphoblastoid cell lines tested. Only one active antibody species could be detected by preparative isoelectric focusing on polyacrylamide gels and by protein-A-Sepharose affinity chromatography. (Author abstract) (17 Refs)

20. SURFACE ANTIGENIC PHENOTYPES OF HUMAN T-CELL LEUKEMIA CORRESPONDING TO THOSE OF POST-THYMIC T CELLS.

Ishii Y, Fujimoto J, Kon S, Ogasawara M, Koshiba H, Mikuni C, Kikuchi K
Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan
Am J Hematol; 12(3):251-260 1982

Leukemic cells from eight adult patients with various types of T-cell leukemias, including one patient with lymphosarcoma cell leukemia (T-LSL), two patients with chronic lymphocytic leukemia (T-CLL), and five patients with adult T-cell leukemia (ATL), were analyzed for their surface antigenic phenotypes with a series of monoclonal antibodies directing to human T-cell differentiation antigens. All of the leukemic T cells studied were regarded as being of post-thymic T-cell origin because of their ability to form rosettes with sheep red cells under the condition at 4 C but not 37 C as well as the expression of human Ly-1-like but not TL-like antigen on their cell surfaces. By using monoclonal antibodies to a variety of human T-cell antigens (Leu-1, Leu-2a, and Leu-3a), all eight cases could be divided into either group of three distinct categories. Thus, one patient with T-LSL had cells with Leu-1+2a+3a+ phenotype, which might reflect possible post-thymic precursor T cells, whereas one patient with T-CLL had cells with the same phenotype (Leu-1+2a+3a-) as normal cytotoxic/suppressor T cells. The latter cells also expressed Ia antigens as defined by monoclonal anti-human Ia antibody. The remaining six cases, including one T-CLL and five ATL patients, had leukemic cells with the same phenotype (Leu-1+2a-3a+) as normally found on helper/inducer T cells, despite distinct clinical and immunological features between T-CLL and ATL. Some clinical findings observed in those patients may reflect functional activities retained by their leukemic T cells. (Author abstract) (34 Refs)

21. SURFACE IMMUNOGLOBULINS ON HAIRY CELLS OF 55 PATIENTS WITH HAIRY CELL LEUKEMIA.

Golomb HM, Davis S, Wilson C, Vardiman J
Box 420, 950 East 59th St., Chicago, IL, 60637
Am J Hematol; 12(4):397-401 1982

Surface immunoglobulins (SIg) were determined on peripheral blood samples from 55 patients with hairy cell leukemia (HCL) and on hairy cells from spleen preparations of 14 of these 55 patients. The patterns of SIg for HCL was compared to the patterns on peripheral blood leukemic cells from 39 patients with chronic lymphocytic leukemia (CLL) and 15 patients with poorly differentiated lymphocytic (PDL) lymphoma. Of the 55 HCL patients, 42 could be scored for individual heavy and light chains; 16 had only IgG, 14 had two or three heavy chains, 7 had only IgD, and 5 cases had no SIg and were E-rosette negative. This pattern was different from the B-cell pattern in CLL and PDL where there were few cases of IgG alone (5%) and many cases of IgM alone (50%). Surface marker profile did not correlate with survival in any of the sub-groups tested. HCL appears to be a B-cell lymphoproliferative disease in greater than 90% of cases; many combinations of heavy chains with only a single light chain can be demonstrated. (Author abstract) (14 Refs)

22. MOUSE ROSETTE (M ROSETTE) IN THE DIFFERENTIAL DIAGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS.

Gabrielli A, Leoni P, Marchegiani G, Montillo M, Centurioni R, Montroni M, Danieli G
Istituto di Patologia Speciale Medica e Metodologia Clinica, Universita di Ancona, Ancona, Italy
Minerva Med; 73(20):1383-1390 1982

The capacity of a subpopulation of human B lymphocytes to form nonimmune rosettes with mouse red blood cells (M rosettes) was used for the differential diagnosis of B-cell lymphoproliferative diseases in 24 patients (12 men and 12 women, 51-77 yr old) with chronic lymphocytic leukemia (CLL), 7 with leukemic lymphoma (LL) and 3 with hairy-cell leukemia (HCL). Four of the 24 patients CLL were in Stage 0, 16 in Stages I-II and 4 in Stages III-IV. The percentages of M rosettes were distinctly increased in the patients with HCL and LL. The percentage of M rosettes remained extremely elevated at lymphocyte counts below 10,000/cubic mm. The absolute counts of lymphocytes carrying this membrane receptor was found to increase with increasing lymphocyte count, which is an expression of the neoplastic population, and with the advancement of the clinical stage according to Rai's classification. (11 Refs) (In ITA)

23. MOUSE RED CELL ROSETTE FORMATION AND THE COLCHICINE SENSITIVITY TEST: RELATIVE USEFULNESS IN THE DIFFERENTIAL DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKAEMIA AND B LYMPHOCYTIC LYMPHOMA.

Sugden PJ, Lilleyman JS
(c/o Lilleyman) Dept. Haematology, Children's Hosp., Sheffield S10 2TH, England
J Clin Pathol; 35(4):376-379 1982

Mouse erythrocyte (M) rosette formation and colchicine sensitivity were compared for their ability to differentiate chronic lymphocytic leukemia (CLL) from B cell non-Hodgkin's lymphoma (NHL) with overspill. Twenty-two cases of CLL and 8 of NHL were studied along with 31 normal adults. Results from the patients in both tests differed significantly from the controls but colchicine sensitivity failed to differentiate them further. M rosettes, on the other hand, while increased in some patients with NHL were, without overlap, much more numerous in those with CLL, and clearly distinguished the two conditions. A significant autolymphocytotoxic effect of plasma from both study groups was also noted which was not found in the controls. (Author abstract) (12 Refs)

24. CLINICAL STUDIES ON IMMUNOPOTENT ACTIVITIES IN THE SERA OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

Iguchi K, Akane H, Tanimoto Y, Matsuda T, Sakurai M, Izawa T, Nishioka K
Dept. Pediatrics, Mie Univ. Sch. Medicine, Tsu, Japan
Rinsho Ketsueki; 23(1):53-60 1982

Immunopotentiating activity of leukemic sera from 35 children with acute lymphoblastic leukemia was investigated with the aid of tests of phytohemagglutinin- (PHA), Concanavalin A-, or pokeweed mitogen-induced lymphocyte blastogenic response and a cell cytotoxicity assay. Prior to treatment of leukemia in the patients, lymphocytes from the peripheral blood of the patients had a lower stimulation index of PHA-blastogenesis rate than did healthy controls. A strong immunosuppressive activity was also observed for the sera from patients with T cell Type leukemia, suggesting that the serum immunosuppressive factors may act specifically on the T cell moiety. Following induction of remission, leukemic sera from patients treated greater than 6 mo enhanced PHA-induced lymphocyte blastogenesis. Leukemic cells that were treated with sera from patients in remission and treated with immunotherapy were cultured with peripheral mononuclear cells. A cytotoxic reaction was observed due to the sera. The enhanced effect due to the sera was associated with the serum level of antibodies against leukemia cells. This suggested that the sera of patients given specific immunotherapy contains antibodies that are a part of antibody dependent cell-mediated immunity. (18 Refs) (In JPN)

25. PHYTOHEMAGGLUTININ OR POKEWEED MITOGEN INDUCTION OF IN VITRO COLONY FORMATION BY T-CELLS FROM PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Pistoia V, Nocera A, Ghio R, Minale P, Ferrarini M
Dept. Immunology, Univ. Genoa, Viale Benedetto XV, 10, 16132 Genoa, Italy
JNCI; 68(2):233-237 1982

The colony-forming capacity of peripheral blood T-cells isolated from B-cell chronic lymphocytic leukemia patients was studied and compared with that of peripheral blood T-cells isolated from two groups of normal controls (young and aged healthy donors). Upon stimulation with phytohemagglutinin or pokeweed mitogen, T-cells from both the patients and the controls developed into colonies but only in the presence of the appropriate conditioned media. When the responses of the three groups were compared, no statistically significant differences were detected. However, the number of patients who failed to respond to phytohemagglutinin was larger than that of normal controls. Studies on a selected group of patients demonstrated that such unresponsiveness was unrelated to the presence of suppressor cells or to inadequate conditions used for stimulation in culture. Rather, this unresponsiveness may be connected with an intrinsic T-cell defect present in certain B-cell chronic lymphocytic leukemia patients. (Author abstract) (33 Refs)

26. PHAGOCYTOSIS AND INTRACELLULAR KILLING BY PERIPHERAL BLOOD MONOCYTES OF PATIENTS WITH MONOCYTIC LEUKEMIA.

van Furth R, Leijh PC, Van Zwet TL, Van den Barselaar MT
Dept. Infectious Diseases, Univ. Hosp., Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands
Blood; 59(6):1234-1238 1982

This article concerns a study on the endocytic functions of circulating monocytes from 12 patients with acute or chronic monocytic leukemia. The results show that phagocytosis and intracellular killing of Staphylococcus aureus are impaired in only two patients and that the opsonic activity of the serum of all patients is normal. With respect to the intracellular killing of ingested Staphylococcus aureus, an interesting phenomenon was found in that the cells of patients with monocytic leukemia proved to be in a state of activation, as shown by the finding that patients' monocytes with normal phagocytosis killed about 64% of the ingested bacteria in the absence of extracellular stimulation by serum factors. When extracellular serum was present, the mean killing index rose to only 69%. This is unlike the situation seen in monocytes from healthy donors, where no killing occurs in the absence of extracellular serum and extracellular stimulation by serum factors is mandatory for optimal intracellular killing. (Author abstract) (9 Refs)

27. INGESTION AND KILLING OF BACTERIA BY NEUTROPHILS FROM PATIENTS WITH LEUKEMIA. A NEW METHOD FOR EVALUATING PHAGOCYTE FUNCTION AT SHORT INCUBATION PERIODS.

Yamamoto K, Sasada M, Nishiyama H, Uchida M, Sawada H, Nakamura T, Maekawa N, Uchino H
Dept. Internal Medicine, Kyoto Univ., Kyoto, Japan
Nippon Ketsueki Gakkai Zasshi; 45(1):56-65 1982

We developed a new method to accurately measure the number of intracellular viable bacteria, making it possible to detect lesser abnormalities of phagocyte function and to examine the function at short incubation periods. The phagocytic and bactericidal capacities of the circulating neutrophils from 13 patients with AML and 16 patients with CML were investigated by our new method. The ingestive capacity for bacteria was impaired in neutrophils from patients with CML. In particular, the impairment was of a higher degree at short incubation periods. The bactericidal capacity of neutrophils from patients with AML was significantly impaired. Higher frequency of the impairment was observed at 15 min of incubation than at 60 min. Four patients with AML were deficient in MPO score. Three of them showed decreased bactericidal capacity at both 15 min and 60 min of incubation. (Author abstract) (35 Refs)

CHEMOTHERAPY

28. HIGH-DOSE CYTOSTATIC TREATMENT IN ACUTE MYELOID LEUKEMIA.

Osterman B, Hardell L, Holm J, Lenner P, Lindholm Ch, Wahlin A
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 79(21):2107-2109 1982

Twenty-six non-pretreated patients (av age 45 yr, 25 patients less than 65 yr old) with acute myeloid leukemia were subjected to high-dose cytostatic therapy. The combination of daunorubicin (DNR: 50 mg/square meter (m2) iv day, 1, 2 and 3, max 100 mg, iv), cytosine arabinoside (ara-C:2 x 80 mg/m2 iv, days 1-6), 6-thioguanine (TG: 140 mg/m2 po, days 1-6) and vincristine (VCR: 2 mg iv, day 1) was used for remission induction therapy. Consolidation therapy consisted of DNR (50 mg/m2 iv, days 1 and 2), ara-C (2 x 80 mg/m2 iv, days 1-5), and TG (140 mg/m2 po, days 1-5) administered during mo 1, 2, 3, 5. After consolidation therapy, treatment consisted of different combinations of DNR (50 mg/m2 iv, day 1), ara-C (80 mg/m2 iv, days 1-3) and TG (140 mg/m2 po, days 1-3) administered during mo 3, 8 and 12. The median survival of all 26 patients was 32 mo (35.5 mo for 17 patients who achieved complete remissions vs 1.5 mo for the 9 other patients who did not). (13 Refs) (In SWE)

29. REMISSION-INDUCTION, CONSOLIDATION AND MAINTENANCE THERAPY BY AVA PROTOCOL IN ACUTE NONLYMPHOBLASTIC LEUKAEMIA.

Torlontano G, Geraci L, Lombardo M, Di Marzio A, Iacone A, Fioritoni G, Bonseni G, Di Bartolomeo P, Ballone E, D'Antonio D, Di Girolamo G, D'Arcangelo L, Pandoli G, Natale D, Spaduno A
Corso Umberto 113, 65100 Pescara, Italy
Haematologica (Pavia); 67(2):230-245 1982

Effects of vincristine (VCR), cytosine arabinoside (Ara-C), and adriamycin (ADR; AVA protocol) were studied in 32 patients (16 males, 16 females, 3-70 yr old, mean 42 yr) with acute nonlymphoblastic leukemia (ANLL) free from severe uncontrollable infections. AVA protocol is described. Maintenance therapy included 6-thioguanine, methotrexate, lomustine, hydroxyurea, cyclophosphamide, and immunotherapy. Remission was observed in 29 (91%) patients; complete remission (CR) was observed in 22 (69%) and partial in 7 (22%) patients. Actuarial estimations of median duration of CR and median survival were 15 mo and 17 mo, respectively, with survival rates of 68 +-9% and 37 +-16% at 12 and 24 mo, respectively. No deaths occurred during CR. Sex, Hb level, total WBC, granulocyte, and platelet count did not appear to influence duration of remission and survival. Survival appeared to be adversely affected by advanced age of patients and also by cell type M6 (erythroleukemia). Most toxic effects occurred during induction and consolidation treatment. Apart from myelosuppression, which occurred after every treatment course but reversed after a 14-20-day therapy-free interval, most frequent toxic manifestations were alopecia, nausea, and vomiting. Infections ranging in severity occurred in more than two thirds of patients, requiring antibacterial drugs and, in 19 patients, granulocyte concentrates. During maintenance therapy, neurotoxic manifestations induced replacement of VCR by vinblastine in most patients greater than 55 yr old. Neural involvement did not compel discontinuance of AVA protocol. AVA therapy is recommended for treatment of acute myelo- and myelomonocytic leukemias; other protocols should be used for other variants of ANLL. (47 Refs)

30. TREATMENT OF REFRACTORY ACUTE NONLYMPHOCYTIC LEUKEMIA WITH A COMBINATION OF PYRAZOFURIN AND CYTARABINE.

Kaplan HG, Appelbaum FR, Choever MA, Greenberg PD, Wood T, Fefer A
Tumor Inst., Swedish Hosp. Medical Center, 1221 Madison St., Seattle, WA, 98104
Cancer Treat Rep; 66(6):1397-1398 1982

Six patients with refractory acute nonlymphocytic leukemia were treated with pyrazofurin (15 mg/m2) followed by cytarabine (100 mg/m2) every 12 hr for 6-21 days. All patients cleared their peripheral blood of blast cells but no complete remissions were achieved. Excessive toxicity to skin and mucous membranes was observed. In the doses used, this combination is too toxic for further use. Alternate treatment schedules should be explored. (Author abstract) (9 Refs)

31. THE EFFECT OF L-ASPARAGINASE ON ANTITHROMBIN, PLASMINOGEN, AND PLASMA COAGULATION DURING THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA.

Priest JR, Ramsay NK, Bennett AJ, Krivit W, Edson JR
Children's Hosp., Incorporated, 345 North Smith Ave., St. Paul, MN, 55102
J Pediatr; 100(6):990-995 1982

Hemostatic function was studied sequentially in 12 children receiving L-asparaginase, vincristine, and prednisone as remission induction chemotherapy for acute lymphoblastic leukemia. The 3-wk period of L-asparaginase therapy was characterized by progressive decreases in plasma antithrombin, plasminogen, and fibrinogen concentrations, and by progressive increases in plasma clotting times (prothrombin time, partial thromboplastin time, thrombin time). Platelet counts rose rapidly during the 3rd and 4th wk of therapy as bone marrow remission was achieved. Factor V levels increased steadily during a 5-wk period, perhaps related to vincristine or prednisone therapy. Recent reports of thrombosis and hemorrhage in children and adults receiving L-asparaginase may be explained by this complex set of abnormalities in coagulation and coagulation control. (Author abstract) (44 Refs)

32. CHEMOTHERAPY SENSITIVITY ASSESSMENT OF LEUKEMIC COLONY-FORMING CELLS WITH IN VITRO SIMULTANEOUS EXPOSURE TO MULTIPLE DRUGS: CLINICAL CORRELATIONS IN ACUTE NONLYMPHOCYTIC LEUKEMIA.

Park CH, Amare M, Morrison FS, Maloney TR, Goodwin JW
Dept. Medicine, Div. Clinical Oncology, Univ. Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS, 66103
Cancer Treat Rep; 66(6):1257-1261 1982

For 13 patients with acute nonlymphocytic leukemia receiving four-drug combination chemotherapy (14 chemotherapy trials), leukemic bone marrow cells were obtained before treatment and were exposed in vitro to all four-drug-mixture solutions simultaneously followed by the survival assessment of leukemic colony-forming cells (L-CFU). Survival of normal marrow colony-forming cells (CFU-C) was also assessed concurrently, and the sensitivity index (SI) of leukemic cells was determined as the ratio of the survival of CFU-C to that of L-CFU. Correlations of in vitro results to clinical results were excellent: four of five trials resulting in complete remission had high SI and eight of nine trials without complete remission had low SI ($p = 0.02$). The potential advantages of this method of

exposing cells to drug mixture are discussed in terms of detecting drug synergism and improving the efficiency of in vitro chemotherapy sensitivity studies. (Author abstract) (11 Refs)

33. EVALUATION OF PLASMA GLUTATHIONE REDUCTASE AS A MARKER DURING DRUG THERAPY IN LEUKEMIA PATIENTS.

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Indian J Cancer; 19(2):93-98 1982

The utility of plasma glutathione reductase (GR) as a marker in diagnosis in different forms of leukemia and as a marker during therapy was determined in 123 patients and 32 controls. In patients, while there was considerable overlap in values of plasma GR, av values were elevated in 78% of 36 with chronic myeloid leukemia (CML), 70% of 30 with acute myeloid leukemia, all 5 with acute monomyeloid leukemia, 2/3 with CML + hairy cell leukemia (HCL), 62% of 29 with acute lymphatic leukemia (ALL), 54% of 13 with chronic lymphatic leukemia (CLL), and 3/5 with HCL. Levels of GR in WBC was noted in 3/5 patients with CLL and 66% of 12 with ALL. A high degree of correlation of WBC count with plasma GR was seen in 11 out of 15 patients studied during therapy. Three patterns of changes were observed in follow-up studies: (1) plasma GR which were high before treatment fell to normal during remission or levels fell during partial response with subsequent rise, (2) in five cases high GR levels were associated with high WBC counts, and (3) in four cases, the GR levels were unrelated to WBC counts. Three case histories of patients with CML are presented in detail. (14 Refs)

34. URINARY 6-HYDROXYMETHYLPTERIN LEVELS ACCURATELY MONITOR RESPONSE TO CHEMOTHERAPY IN ACUTE MYELOBLASTIC LEUKEMIA.

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Cancer; 50(1):114-117 1982

In our earlier study it was shown that patients with various types of cancer excrete 3-to 20-fold higher levels of urinary 6-hydroxymethylpterin as compared to patients with nonmalignant disease or normal volunteers. In the present study urinary 6-hydroxymethylpterin levels have been measured as an index of disease status in acute myeloblastic leukemic patients on antileukemic drugs. The daily excretory pterin levels and the values of respective blast counts have been graphically presented for four cases with the chemotherapeutic regimens. Remission of the disease was marked by a rapid drop in the urinary 6-hydroxymethylpterin levels and correlated very well with the percentage of blasts. In another study the percentage of blasts and the urinary 6-hydroxymethylpterin were determined simultaneously in four patients undergoing chemotherapy. The data conclusively show that the simple noninvasive determination of urinary 6-hydroxymethylpterin levels accurately and rapidly reflects the status of the disease under treatment and could conveniently be employed as a suitable index for monitoring the effect of chemotherapy as well as the condition of the residual extramedullary leukemic infiltration. (Author abstract) (10 Refs)

35. HISTOLOGICAL STUDY OF SERIAL BONE MARROW BIOPSY DURING CHEMOTHERAPY OF ACUTE GRANULOCYTIC LEUKEMIA.

Okita H, Block M

Div. Internal Medicine, Res. Inst. for Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan

Nippon Ketsueki Gakkai Zasshi; 45(3):562-578 1982

Histopathology of chemotherapeutic induction of remission was studied in serial bone marrow sections of 57 patients with acute granulocytic leukemia. The patients were treated with various protocols using combinations of the following drugs: 6-mercaptopurine, prednisone, methotrexate, cytosine arabinoside, 6-thioguanine, vincristine, daunorubicin, and adriamycin. The histopathological changes that occurred during remission induction were divided into two overlapping phases: decrease of the leukemic tissue and recovery of the normal hematopoietic tissue or leukemic tissue. During the period of maximal depletion of leukemic tissue, which usually occurred 7-15 days after the end of the first course of induction therapy, osteoblast proliferation was observed against a background of bone marrow containing plasmacytes, lymphocytes, and serous fat atrophy. Leukemic tissue was 95% decreased in 35/57 patients. Regeneration of normal tissue began 10-20 days after termination of therapy in 28 patients and was characterized by appearance of large, irregularly distributed islands of proliferating basophilic intermediate megaloblasts and megakaryocytes. Regeneration of both normal and leukemic tissue was observed in 7/35 patients, and overt leukemia was observed in 5/7 within several weeks. A 95% depletion of leukemic tissue without a long aplastic phase of therapy and prophylactic treatment for infection and hemorrhage during the aplastic phase were thought to be important factors in improving remission rates. (64 Refs) (In JPN)

SURGERY

36. SURGICAL COMPLICATIONS AND FULMINANT INFECTIONS FOLLOWING ELECTIVE SPLENECTOMY FOR HEMATOLOGICAL DISEASE. RETROSPECTIVE REVIEWS OF A 10-YR PERIOD.

Sakso P, Nielsen JL, Sorensen FH

Kirurgisk afdeling 1, Arhus amtssygehus, Arhus, Denmark

Ugeskr Laeger; 144(20):1459-1461 1982

The incidence of postoperative complications were studied in 94 consecutive patients subjected to elective splenectomy for hematological diseases, including eight with chronic lymphocytic leukemia (CLL), five with chronic myeloid leukemia (CML), eight with malignant lymphoma (ML), five with hairy-cell leukemia (HCL), and five with Hodgkin's disease (HD). Forty-two of the 94 patients, including 1/8 with ML and 1/5 with HCL were subjected to preoperative corticosteroid therapy, 18/94, including 5/8 with CLL, 5/5 with CML, 1/8 with ML and 1/5 with HD to preoperative cytostatic treatment. Splenomegaly was found in 30/94 patients, including in 5/8 with CLL, 5/5 with CML, 8/8 with ML, 2/5 with HCL and 1/5 with HD. The incidence of postoperative complications was 31/94 (5/8 with CLL, 4/5 with CML, 3/8 with ML, 1/5 with HCL and 1/5 with HD). The complications included intraoperative and postoperative hemorrhages, temperatures above 38.5 C for more than 3 days, sepsis, abdominal abscess, pulmonary affections, and wound infection. Fulminant infections following splenectomy occurred in 3/94 patients (all chil-

dren), which was lethal in 2/3, who were treated with immunosuppressive agents or cytostatics after splenectomy. The postoperative mortality was 3/94, including one patient each with CLL and CML. Administration of polyvalent pneumococcal vaccine is recommended prior to splenectomy. (13 Refs) (In DAN)

MULTIMODAL THERAPY

37. CRANIAL COMPUTED TOMOGRAPHY DURING TREATMENT OF CHILDHOOD LYMPHOCYTIC LEUKEMIA.

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Acta Paediatr Scand; 71(2):257-262 1982

Twenty-three children with acute lymphocytic leukemia (ALL) were examined by computed tomography (CT) of the head on two occasions more than 11 months apart. The first CT was performed at the time of diagnosis in 11 children, who were re-examined while still in their first complete remission. They had received prophylactic central nervous system (CNS) treatment consisting of intrathecal methotrexate supplemented by irradiation in seven cases and intermediate dose methotrexate in four cases. Twelve children were receiving treatment for CNS relapse. This included therapeutic irradiation and intrathecal methotrexate. Abnormal CT developed in seven children. Three CT scans demonstrated areas of decreased attenuation coefficient, one with intracerebral calcifications. In five patients, dilatation of the ventricles and cortical sulci had developed. All CT abnormalities occurred in children in remission after CNS relapse. These results indicate that prophylactic treatment including cranial irradiation with 24 Gy and low cumulative doses of methotrexate is a safe procedure. Patients with CNS leukemia are at risk of developing CNS abnormalities, when they receive treatment with cranial irradiation and methotrexate. The risk is not correlated with age or sex of the child, the duration of the disease, the dose of irradiation or the cumulative dose of methotrexate. (Author abstract) (20 Refs)

38. TESTICULAR RELAPSE IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDREN.

Fujiu M, Bessho F
Dept. Pediatrics, Tokyo Univ., Tokyo, Japan
Rinsho Ketsueki; 23(1):33-39 1982

Occurrence of testicular relapse was studied in 51 boys with acute lymphocytic leukemia that was treated with chemotherapy. Induction chemotherapy consisted of either high dose steroid hormones (SH; prednisolone), high dose SH + vincristine (VCR), or normal dose SH + VCR. The testicular leukemia was treated with SH + VCR or chemotherapy and ipsilateral or bilateral testicular radiotherapy. Of the 51 patients, 43 achieved complete remission, and 17/43 had testicular relapse. There was no significant difference in the rates of testicular relapse between the group of patients who received the large dose SH and those who received the normal dose SH. However, the period of remission prior to relapse was significantly longer (av 53.1 mo vs 19.1 mo) for the patients given the large dose than those given the normal dose. Prognosis for testicular relapse was poor. A policy for prevention of testicular leukemia as the first relapse included detecting occult leukemic infiltration in biopsy specimens and early stage local treatment with reinduction therapy. (22 Refs) (In JPN)

SUPPORTIVE CARE

39. INDICATIONS FOR PLATELET TRANSFUSION IN CHILDREN WITH ACUTE LEUKEMIA.

Murphy S, Litwin S, Herring LM, Koch P, Remischovsky J, Donaldson MH, Evans AE, Gardner FH
Cardeza Foundation Hematologic Res., 1015 Walnut St., Philadelphia, PA, 19107
Am J Hematol; 12(4):347-356 1982

In an attempt to determine the indications for platelet transfusion in thrombocytopenic patients, we randomized 56 children with acute leukemia to one of two regimens of platelet transfusion. The prophylactic group received platelets when the platelet count fell below 20,000 per mm3 irrespective of clinical events. The therapeutic group was transfused only when significant bleeding occurred and not for thrombocytopenia alone. the time to first bleeding episode was significantly longer and the number of bleeding episodes were significantly reduced in the prophylactic group. The survival curves of the two groups could not be distinguished from each other. Prior to the last mo of life, the total number of days on which bleeding was present was significantly reduced by prophylactic therapy. However, in the terminal phase (last mo of life), the duration of bleeding episodes was significantly longer in the prophylactic group. This may have been due to a higher incidence of immunologic refractoriness to platelet transfusion. Because of this terminal bleeding, comparison of the two groups for total number of days on which bleeding was present did not show a significant difference over the entire study period. (Author abstract) (6 Refs)

40. TRIMETHOPRIM-SULFAMETHOXAZOLE IN THE TREATMENT OF ADULTS WITH PNEUMONIA DUE TO PNEUMOCYSTIS CARINII.

Young LS
Div. Infectious Diseases, Dept. Medicine, Univ. California, Los Angeles, CA, 90024
Rev Infect Dis; 4(2):608-613 1982

Use of oral or iv trimethoprim-sulfamethoxazole (TMP-SMZ) for the treatment of pneumonia due to Pneumocystis carinii in a total of 19 patients is reported. Five patients were recipients of organ transplants, four had acute lymphatic leukemia, two had collagen vascular disease, and four had other underlying diseases treated with corticosteroids. All patients had diffuse pneumonitis, tachypnea, and dyspnea, and all but one were hypoxic. Oral doses were 20 mg of TMP/day plus 100 mg SMZ/kg/day in two or three divided doses. Iv doses were 10-15 mg/kg/day divided into three or four doses, adjusted to maintain a postinfusion level of greater than 5 ug/ml of serum. Of the eight patients given po TMP-SMZ, four were clinically cured, one responded clinically but had persistent pulmonary infiltrates (autopsy revealed metastatic carcinoma but no P carinii infection), one died without autopsy, and two died with evidence of persistent pneumocystosis. Both the latter patients had levels of TMP in serum less than 1.5 ug/ml. Of the six patients treated with po drugs for nine or more days, five were cured. Of the 12 patients given iv drugs, 8 were clinically or microbiologically cured, two died with rapidly progressing pneumonitis, and two others failed. Of the four failures, three had other serious infections. The fourth failure represented the only case in which TMP-SMZ failed to cure pneumonia due to P carinii; subsequent administration of pentamidine resulted in cure. One pediatric patient given iv drugs initially failed to achieve a postinfusion level of greater than 5 ug/ml and re-

quired a daily dose of 30 mg/kg to reach the target level. No serious side effects occurred. Review of the literature demonstrates that treatment of pneumocystis pneumonia with TMP-SMZ produces a better response rate and fewer side effects than pentamidine. (24 Refs)

41. TRIMETHOPRIM-SULFAMETHOXAZOLE AND TRIMETHOPRIM ALONE FOR PROPHYLAXIS OF INFECTION IN GRANULOCYTOPENIC PATIENTS.

Gurwith M, Truog K, Hinthorn D, Liu C
Dept. Medicine, Michigan State Univ., B220 Life Sciences, East Lansing, MI, 48824
Rev Infect Dis; 4(2):393-601 1982

Prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMZ) or TMP alone for prevention of infection in neutropenic patients is reviewed. When given on a long term basis to children with acute leukemia in order to prevent Pneumocystis carinii infections, a decrease in the number of bacterial infections was observed. The TMP-SMZ group had a significant reduction in the number of infectious episodes, especially bacteremia: no cases occurred in 59 episodes of granulocytopenia vs 9 cases in 7 patients during 59 granulocytic episodes given no prophylactic antibiotics. In addition, the percentage of granulocytopenic days and the usage of parenteral antibiotics in the TMP-SMZ group was significantly lower compared with controls. Investigations of TMP-SMZ in granulocytopenic patients have confirmed that TMP-SMZ is useful in preventing infection. For prophylaxis in granulocytopenic patients, TMP appeared to be as effective as TMP-SMZ in both efficacy and incidence of side effects. However, TMP was less effective in suppressing gastrointestinal flora, including TMP-resistant gram-negative rods. Prophylaxis by TMP-SMZ is explained by suppression of gram-negative rods, by its lethal action against many Enterobacteriaceae in the gastrointestinal tract and suppression of invasion by surviving Enterobacteriaceae, and by its ability to decrease bacterial adherence. (25 Refs)

42. DENTAL EXTRACTIONS IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKEMIA.

Overholser CD, Peterson DE, Bergman SA, Williams LT
Baltimore Coll. Dental Surgery, Dental Sch., Univ. Maryland at Baltimore, Baltimore, MD, 21201
J Oral Maxillofac Surg; 40(5):296-298 1982

Dental extractions in patients with leukemia are controversial, since they may lead to hemorrhage, delayed wound healing, and infection. However, the retention of diseased teeth in these patients may also lead to infectious complications during chemotherapy. With adequate hematologic values and specific surgical techniques, 119 extractions were performed on 28 patients with acute nonlymphocytic leukemia. No serious adverse sequelae occurred, and the prevalence of other adverse effects was comparable with that in nonleukemic patients. It is concluded that with proper precautions, extractions can be performed on these patients. (Author abstract) (11 Refs)

43. ENTERAL NUTRITION BY NASOGASTRIC TUBE IN ADULT PATIENTS TREATED WITH INTENSIVE CHEMOTHERAPY FOR ACUTE LEUKEMIA.

de Vries EG, Mulder NH, Houwen B, De Vries-Hospers HG
Div. Hematology, Dept. Medicine, Univ. Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands
Am J Clin Nutr; 35(6):1490-1496 1982

In this study, nutritional status 3 wk after starting 20 induction courses of chemotherapy with enteral nasogastric tube feeding was compared to the nutritional status after 35 courses with a normal oral hospital diet. Tube feeding consisted of 2,000 to 3,000 cal daily of a hospital made pasteurized formula or sterile Nutrison RTS. In the group fed by nasogastric tube the mean wt loss was significantly smaller (p less than 0.01) and there were fewer patients with a severe wt loss of more than 5% during the 1st 3 wk (p less than 0.01) than in the hospital diet group. Serum albumin reduction of more than 10% was present in 4/20 and 23/35 for each group respectively (p less than 0.01). Bacterial contamination occurred in the pasteurized hospital-made formula which led to Pseudomonas septicemia in one patient. During a short-term catabolic state (3 wk) sterile feeding by nasogastric tube can prevent wt loss and hypoalbuminemia in most patients. Bacteriological control of the food and supply system is mandatory in granulocytopenic patients. (Author abstract) (20 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

44. HEMATOPOIETIC DYSPLASIA AND MARROW HYPOCELLULARITY IN CHILDREN: A PRELEUKEMIC CONDITION.

Kobrinsky NL, Nesbit ME, Ramsay NK, Arthur DC, Krivit W, Brunning RD
(c/o Brunning), Univ. Minnesota, Box 198, Mayo Memorial Building, 420 Delaware St. S.E., Minneapolis, MN, 55455
J Pediatr; 100(6):907-913 1982

Seven children with hematopoietic dysplasia were identified by morphologic criteria. The peripheral blood and bone marrow findings in these children were characterized by macro-ovalocytosis, progressive marrow hypoplasia, proteinaceous debris in the marrow interstices, and megaloblastoid changes. Six of the patients had major constitutional abnormalities including coarse or unusual facies (4), short stature (4), and mental retardation (4). These children were prone to recurrent bacterial infections prior to the onset of documented leukopenia. Chromosome studies of blood and bone marrow demonstrated a clonal abnormality involving the B, C, and E groups in 3/5 patients. An increase in the number of spontaneous chromosome breaks or radial figures was not observed. CFU-Cs were uniformly decreased in 5/5 patients, prior to the onset of leukopenia in one. Incomplete and transient responses to folic acid (3/4), androgens (1/4), and steroids (3/3) were noted. There were no responses to vitamin B12 in three patients or to ATG or other immunosuppressive therapies in four patients. One child has a sustained response to pyridoxine and one has had successful hematopoietic reconstitution by bone marrow transplantation. Three of the patients developed myelogenous leukemia 13, 47, and 100 mo, respectively after presentation. Two have died from leukemia and one from intracranial hemorrhage. Children with HD differ morphologically and clinically from adults with 'the preleukemic syndrome' by manifesting marrow hypocellularity and constitutional abnormalities. Both groups are at high risk for the development of progressive pancytopenia and myelogenous leukemia. Unlike those with Fanconi anemia, these children respond poorly to treatment with androgens and steroids. Results of bone marrow transplantation in one of the patients are encouraging. (Author abstract) (20 Refs)

45. ANTIBODIES TO ADULT T-CELL LEUKEMIA-VIRUS-ASSOCIATED ANTIGEN (ATLA) IN SERA FROM PATIENTS WITH ATL AND CONTROLS IN JAPAN: A NATION-WIDE SERO-EPIDEMIOLOGIC STUDY.

Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, Kikuchi M, Ichimaru M, Yunoki K, Sato I, Matsuo R, Takiuchi Y, Uchino H, Hanaoka M

Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan

Int J Cancer; 29(6):631-635 1982

A nation-wide sero-epidemiologic survey of adult T-cell leukemia virus (ATLV), detected as anti-ATLA (ATLV-associated antigen), was made in Japan. Sera from adult donors in 15 different locations were screened for anti-ATLA. High incidences (6 to 37%) of antibody-positive donors were found in seven regions, one in northern Japan, and the others in southwestern regions. These areas are ATLV-endemic areas corresponding to ATL-endemic areas. Examination of sera from healthy donors aged 6 to 80 yr in ATL-endemic areas showed an age-dependent increase of seropositive donors with a maximum of about 30% to 40 yr of age. Anti-ATLA was found in all but two of 142 patients with ATL. Anti-ATLA-positive patients with ATL were mainly found in ATLV-endemic areas and only a few in ATL-nonendemic areas. Six patients with cutaneous T-cell lymphoma in ATLV-nonendemic areas gave a negative reaction for anti-ATLA. The geometric mean titer of anti-ATLA of patients with ATL was higher than that of healthy donors. (Author abstract) (9 Refs)

SELECTED PRE-CLINICAL STUDIES

46. ACTIVITY OF 2-FLUORO-5-METHYLARABINOFURANOSYLURACIL AGAINST MOUSE LEUKEMIAS SENSITIVE TO AND RESISTANT TO 1BETA-D-ARABINOFURANOSYLCYTOSINE.

Burchenal JH, Chou TC, Lokys L, Smith RS, Watanabe KA, Su TL, Fox JJ

Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

Cancer Res; 42(7):2598-2600 1982

A new pyrimidine nucleoside, 2'-fluoro-5-methyl-1-beta-D-arabinofuranosyluracil, previously has been shown to be active against the herpes group of viruses in vitro and in vitro. It is also active against mouse and human leukemic cells in culture and against mouse leukemias L1210, P388, and P815 in vivo. In contrast to other 1-beta-D-arabinofuranosylcytosine (ara-C) derivatives, 2'-fluoro-5-methyl-1-beta-D-arabinofuranosyluracil, when given either ip or po, is highly active against lines of leukemias P815 and L1210 made resistant to ara-C. Against P815/ara-C and L1210/ara-C, it is more effective than is 5-azacytidine, a drug which has shown definite effectiveness in patients with acute leukemia whose disease has become resistant to ara-C. For these reasons, 2'-fluoro-5-methyl-1-beta-D-arabinofuranosyluracil would seem to merit clinical trial in patients with acute nonlymphocytic leukemia whose disease has become resistant to ara-C. (Author abstract) (10 Refs)

47. METABOLISM AND THERAPEUTIC EFFICACY OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE AGAINST MURINE LEUKEMIA P388.

Avramis VI, Plunkett W

(c/o Plunkett) Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Cancer Res; 42(7):2587-2591 1982

The biochemical basis for the differential therapeutic activity of equally toxic doses of 9-beta-D-arabinofuranosyl-2-fluoroadenine (F-ara-A) administered on two schedules to tumor-bearing mice has been studied. A single dose (234 mg/kg) of F-ara-A in solution decreased the number of P388 leukemia cells by greater than 10(3), whereas a multiple-dose regimen (41 mg/kg every day for 5 days) of equal toxicity to the host was ineffective at reducing the tumor burden. No antitumor activity was seen when an equal dose of the relatively insoluble F-ara-A was injected as a suspension. The 5'-triphosphate of F-ara-A accumulated in P388 cells in levels proportional to the dose of the nucleoside and disappeared from these cells at an exponential rate with a half-life of 2.9 hr, which was independent of the cellular concentration of the nucleotide. The extent and duration of the inhibition of DNA synthesis of P388 cells was dependent on the dose of F-ara-A, but the rates of recovery were similar and in proportion to the cellular concentration of the analog triphosphate. The extent of the inhibition of DNA synthesis in host bone marrow and intestinal mucosa was also related to the dose of F-ara-A, but the recovery of these tissues proceeded to similar, incomplete levels (less than 60% of initial) 24 hr after F-ara-A injection of either 41 or 234 mg/kg. These results suggest that the equal toxicity of the two regimens of F-ara-A may be attributed to the similar extent of inhibition of host-tissue DNA synthesis evoked by each. In contrast, the greater extent and longer duration of inhibition of P388 cell DNA synthesis caused by the single dose of F-ara-A was responsible for its superior therapeutic activity. Measurements of F-ara-A triphosphate concentrations and the DNA-synthetic capacity of tumor and host tissues are determinants of the action of F-ara-A and may be used to predict optimal therapeutic dose schedules. (Author abstract) (23 Refs)

REVIEWS

48. ACUTE LYMPHOBLASTIC LEUKEMIA.

Chessells JM

Dept. Hematology, Hosp. Sick Children, Great Ormand St., London WC1N 3JH, England

Semin Hematol; 19(3):155-171 1982

Recent advances in the classification, diagnosis, prognosis and treatment of acute lymphoblastic leukemia are reviewed. Three types of acute lymphoblastic leukemia and six types of acute myeloblastic leukemia are presently recognized, although immunologic classification is showing increasing promise and may lead to refined diagnosis. Prognostic factors include basic clinical and hematological data, morphological features, immunological features, cytogenetics, and sex of the patient. Remission is readily achieved in most children with ALL. The combination of prednisolone and vincristine alone is successful in 85-90% of patients. With the addition of L-asparaginase the rate rises to 93%. The most important question, as yet unresolved, is whether the use of additional drugs during induction, or of a period of subsequent intensive consolidation chemo-

therapy, increases the chances of long-term hematologic remission. Relevant studies are discussed. Continuing maintenance therapy is an essential component of treatment for acute lymphoblastic leukemia, although the optimum type and duration of treatment are as yet unidentified. Specifics of present maintenance programs, immunotherapy, duration of chemotherapy, marrow relapse, extramedullary leukemia, prevention and treatment of CNS leukemia, CNS prophylaxis, testicular infiltration, complications of therapy, and speculation concerning future developments are among other topics discussed. (213 Refs)

49. CHROMOSOMAL ABERRATIONS IN CHRONIC B-CELL LYMPHOCYTIC LEUKEMIA.

Gahrton G, Robert KH
Dept. Medicine, Karolinska Inst., Huddinge Univ. Hosp., S-141 86 Huddinge, Sweden
Cancer Genet Cytogenet; 6(2):171-181 1982

Production, incidence, and types of chromosome aberrations in chronic B-cell lymphocytic leukemia (B-CLL) are reviewed. Of polyclonal B-cell mitogens, Epstein-Barr virus and lipopolysaccharide from E coli have been the most successful for cytogenetic analysis of B-CLL. The mitogenic responses measured by 3H-labeled thymidine incorporation into leukemic cells and the mitotic index are variable. Difficulties associated with calculating reliable incidence figures for chromosomal aberrations in B-CLL are considered. In B-CLL, both numerical and structural aberrations are found. The most common numerical aberration is an extra chromosome 12. Other aberrations include deletion of chromosome 14, translocations, deletions, and other extra chromosomes. Many of the chromosomal abnormalities seen in B-CLL have also been found in other malignant hematopoietic disorders, particularly lymphoproliferative disorders. However, the most common abnormality, the extra chromosome 12, is rare in other disorders. The biological significance and prognostic importance of chromosomal aberrations in B-CLL are discussed. (72 Refs)

50. THE TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA IN ADULTS.

Lister TA, Rohatiner AZ
Dept. Medical Oncology, St. Bartholomew's Hosp., West Smithfield, EC1A 7BE, England
Semin Hematol; 19(3):172-192 1982

The diagnosis of acute myelogenous leukemia (AML), the development of curative chemotherapy, and factors influencing prognosis are reviewed. It is currently possible to induce complete remission in most AML patients. Median duration of remission has been prolonged, and a sufficient number of patients have been in remission for more than 5 yr for cure to be anticipated. Diagnosis (morphology and cytochemistry, surface phenotype and enzyme markers, bone marrow cellularity), anti-leukemic therapy, the achievement of complete remission (single agent therapy, the anthracycline antibiotics, combination chemotherapy), the achievement of prolonged remission and possible cure, and prognostic factors (advanced age, presence of infectious complications and thrombocytopenia, inadequate supportive care, abnormalities of peripheral blood or bone marrow, rate of DNA synthesis, and the behavior of leukemic blast cells in culture) are discussed in detail. Future applications of predictive assays may allow early discrimination of responding vs nonresponding patients. (137 Refs)

51. BONE MARROW TRANSPLANTATION IN ACUTE LEUKEMIA.

Santos GW, Kaizer H
Oncology Center 3-127, Johns Hopkins Hosp., 600 North Wolfe St., Baltimore, MD, 21205
Semin Hematol; 19(3):227-239 1982

The current status of the use of both allogeneic and syngeneic bone marrow transplantation in producing long-term leukemia control and cure is reviewed. The use of bone marrow transplantation provides two potential therapeutic advantages over standard chemotherapeutic approaches. First, it enables the extension of intensity of cytoreductive therapy without regard to hematopoietic toxicity since the infusion of marrow is able to rescue the patient from otherwise lethal therapy. This procedure eliminates the relative refractoriness of leukemic cells to standard cytotoxic agents by increasing dose. Second, post-transplant changes in immunoregulatory processes, particularly those associated with graft-versus-host disease, may provide post-transplant immunotherapeutic effects against residual tumor. Indications for, success with, and problems associated with allogeneic marrow transplantation, syngeneic marrow transplantation, and autologous marrow transplantation are discussed. Post-transplant infections, interstitial pneumonitis and acute graft-versus-host disease, the most serious threats to marrow transplant recipients, particularly those receiving allogeneic transplants, are reviewed. Bone marrow transplantation is a viable alternative to current non-transplant treatment regimens in acute leukemia, especially acute nonlymphocytic leukemia. (114 Refs)

52. INFECTIOUS COMPLICATIONS IN LEUKEMIC PATIENTS.

Bodey GP, Bolivar R, Fainstein V
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Semin Hematol; 19(3):193-226 1982

Recent advances in understanding the pathobiology of infectious complications occurring in patients with acute leukemia, their respective prognoses and their treatment are reviewed. Topics discussed include factors associated with infection (leukopenia, abnormal neutrophil function, myelosuppression), new organisms and changing patterns of infection (Staphyloccoccus aureus, S epidermis, legionella pneumophila, JK bacteria, Corynebacterium species, Clostridium difficile, Capnocytophaga ochracea) approaches to diagnosis of infection (bacterial, fungal, viral), management of infection (antibiotic schedule, antibiotic synergism, new antibiotics, antifungal and antiviral agents), and prophylaxis of infection (granulocyte transfusion, bone marrow transplantation, lithium carbonate, immunotherapy, Pseudomonas vaccine, pneumococcal polysaccharide vaccine, cytomegalovirus vaccine, varicella zoster vaccine, passive immunotherapy, hepatitis immune globulin, antisera to gram-negative bacteria, transfer factor, interferon, immunomodulators). (256 Refs)

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ACUTE AND CHRONIC LEUKEMIA

Diagnosis, Treatment

SERIES CT03 No. 82/12 DECEMBER, 1982

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DIAGNOSIS

1. PROGNOSTIC SIGNIFICANCE OF TERMINAL TRANSFERASE ACTIVITY AND OTHER FACTORS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

Hutton JJ, Coleman MS, Moffitt S
Dept. Medicine, Univ. Texas, San Antonio, TX
Adv Exp Med Biol; 145:243-257 1982

Activity of terminal deoxynucleotidyl transferase (TdT) was measured in cells from the bone marrow and peripheral blood of 206 children (less than 1-16 yr old, av 77 mo) with acute lymphoblastic leukemia (ALL) to investigate the prognostic significance of the quantitative variations in level of TdT at diagnosis and to find out whether quantitative measurements of TdT activity during remission of leukemia can predict relapse of disease. Complete remission (CR) was obtained in 96% of patients, and 43% relapsed during the course of the study. The median duration of CR was 1,400 days. Maintenance chemotherapy was generally continued for 3 yr after complete remission was achieved or until relapse occurred. The mean TDT activity in the bone marrow of 157 patients was 91 +-143 units (U)/10(8) cells. For peripheral blood the mean activity was 54

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+-159 U/10(8) cells of 163 specimens. The large standard deviation reflects the wide range of activities seen in patients with ALL. A significant proportion of the variation was due to a relatively small number of patients with extremely high activities. The bone marrow from 198 children without ALL contained 5.9 U of TdT activity/10(8) cells with a standard deviation of TdT measurements could not be used to predict malignancy because significant overlap of the two groups was observed. Results showed that the quantitative activity of TdT in blasts at diagnosis of children with typical ALL does not convey prognostic information. (5 Refs)

2. THE PROGNOSTIC SIGNIFICANCE OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE (TDT) IN PATIENTS WITH LEUKEMIAS AND MALIGNANT LYMPHOMAS.

Mertelsmann R
Developmental Hematopoiesis Lab., Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Adv Exp Med Biol; 145:259-277 1982

Activity of terminal deoxynucleotidyl transferase (TdT) was analyzed and the relationship to remission frequency and duration as well as survival in patients with acute lymphoblastic leukemia (ALL), acute nonlymphoblastic leukemia (ANLL), and malignant-non-Hodgkin's lymphoma (NHL) in adults was investigated. All patients were diagnosed and treated according to standardized chemotherapy protocols. Of 113 patients treated on ALL protocols including 101 patients with ALL and 12 patients with lymphoblastic lymphoma, 44 patients were studied for TdT activity at diagnosis prior to treatment and an additional 38 patients after initiation of treatment or at relapse. Of 72 patients with evaluable TdT determinations, only 2 with B cell ALL and 1 with T cell ALL failed to exhibit elevated TdT activities. Pre-treatment bone marrow TdT activities were found to be significantly related to survival: patients exhibiting TdT activities less than 1 unit (U)/10(8) cells showed the longest survival. Thirteen of 91 patients with ANLL receiving chemotherapy exhibited elevated TdT activities as observed in ALL and 11 (12%) exhibited low (less than 0.1 U/10(8) cells) but unequivocal TdT activity. Of 52 patients with diffuse NHL treated with protocol chemotherapy, 50% of null cell lymphomas and 52% of T cell lymphomas exhibited high levels of TDT activity. These findings documented the prognostic significance regarding survival of levels of TDT activity in ALL, ANLL, and diffuse NHL. (32 Refs)

3. NUCLEAR TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE (TDT) IN LEUKEMIC INFILTRATES OF TESTICULAR TISSUE.

Janossy G, Thomas JA, Eden OB, Bollum FJ
Dept. Immunology, Royal Free Hosp., London, England
Adv Exp Med Biol; 145:321-330 1982

Indirect immunofluorescence (IF) and immunoperoxidase (IP) techniques were used to determine the optimal method for identifying terminal deoxynucleotidyl transferase (TdT) positive leukemic blasts in 40 testicular biopsies. In 11 patients the routine histology of testicular biopsies (taken as routine procedure or for clinical suspicion) showed heavy leukemic infiltrates. In nine of these patients strong nuclear TdT staining was observed in the infiltrating lymphoblasts while in two patients cells were present but were TdT negative. In some patients the leukemic blasts were heterogeneous and some contained no identifiable TdT enzyme in the vicinity of strongly positive blasts. The TdT positivity corresponded to the nucleus and clear cytoplasmic staining was observed only in the dividing cells where TdT is known to be released from the disrupted nucleus. In seven biopsies from patients with treated acute lymphoblastic leukemia (ALL) the normal structure of seminiferous tubules was preserved and no histological evidence of increased lymphoid or lymphoblastic infiltration was observed. Large areas of the tissue were void of TdT positive cells. No identifiable TdT positive cells were present in another seven testicular biopsies from patients with treated ALL. With one exception all patients were regarded at the histological investigation as apparently non-involved samples. (14 Refs)

4. ENRICHMENT OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY BY CELL SEPARATION.

Sarin PS, Virmani M, Gallo RC
Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Adv Exp Med Biol; 145:337-356 1982

The technique of free flow electrophoresis was utilized for separation of human leukemic cells into terminal deoxynucleotidyl transferase (TdT) positive cell populations. With the technique, an up to 20-fold enrichment in TdT positive cells was obtained thus making the detection of low levels of enzyme simpler, and providing a tool for selection and identification of cell types containing the enzyme for biochemical and biological studies. With the use of the technique enrichment of TdT positive cell populations from normal human bone marrow, cells from patients with acute lymphoblastic leukemia, and chronic myelogenous leukemia in blast phase of the disease were enriched. (27 Refs)

5. CLINICAL RELEVANCE OF TERMINAL TRANSFERASE AD ADENOSINE DEAMINASE IN LEUKEMIA.

Brusamolino E, Bertazzoni U, Isernia P, Ginelli E, Scovassi AI, Zurlo MG, Plevani P, Sacchi N, Bernasconi C
Divisione di Ematologia, Policlinico S. Matteo, Pavia, Italy
Adv Exp Med Biol; 145:279-303 1982

Correlation between terminal deoxynucleotidyl transferase (TdT) and adenosine deaminase (ADA) was investigated in 119 adults and 63 children with acute leukemia at presentation, 40 patients with acute lymphoblastic leukemia (ALL) at clinical relapse, 90 patients with acute leukemia in clinical remission, 42 adults with Philadelphia chromosome-positive (Ph'+) chronic myelocyte leukemia (CML) in chronic phase, 28 adults with Ph'+ CML in blastic phase, 3 patients with Ph'+ acute leukemia presenting as ALL, and 15 non-neoplastic human controls. All seven T-ALL adults were positive for TdT, whereas the three B-ALL adults were TdT negative; 26/28 non-T, non-B ALL patients were TdT positive. In children, TdT was positive in 8/9 patients with T-ALL and in 35/41 with non-T, non-B ALL; the single B-ALL patient was TdT negative. The ADA enzymatic assay was performed in 27 adults and 9 children with ALL. The range of ADA varied between 20-7,580 units (U)/10(8) cells, with a mean of 1,458 +-393 U/10(8) cells in adults and 745 +-334 U/10(8) cells in children; a mean of 113 +-16 was found in non-neoplastic controls. The TdT enzymatic assay was strictly negative in the peripheral blood of 18 Ph'+ leukemia patients. The av value of ADA activity in Ph'+ leukemias in stable phase (25 patients) was 103 +-15 U/10(8) cells, which was very close to that obtained for 10 non-neoplastic controls. The values of ADA were increased over the controls only in two patients showing early signs of transformation. (28 Refs)

6. TDT-POSITIVE AND TDT-NEGATIVE HUMAN LEUKEMIC CELLS: SPECIFIC DENSITY AND MORPHOLOGY.

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Adv Exp Med Biol; 145:357-370 1982

Cell density distribution of normal terminal deoxynucleotidyl transferase (TdT) positive bone marrow cells was compared with that of TdT positive leukemic blast cells to study the nature of the leukemic populations. Ultrastructural features of cell fractions expressing or not expressing the marker in the different leukemias were examined. In 10 untreated patients with Philadelphia chromosome (Ph1) positive chronic myeloid leukemia (CML) studied at the onset of the disease, no TdT activity was observed. One of the patients underwent a TdT positive blastic crisis 8 mo later, suggesting that TdT positive cells arise, at least in a sizable number at the onset of the blastic crisis and then accumulate rapidly. TdT was evaluated in 31 patients during the blastic crisis of CML and in 3 patients undergoing the blastic transformation following other myeloproliferative disorders. Fourteen CML-blastic crisis TdT positive cells were found in 14 CML-blastic crisis patients, the involved lymph nodes in one additional patient, and in the lymph nodes of a patient with agnogenic myeloid metaplasia in blastic proliferation. Three TdT positive and two TdT negative patients were Ph1 negative. No correlation between TdT-positivity and length of chronic phase was observed. A total of 67 patients with acute lymphoid leukemia were studied during a 3-yr period. Nine of 10 TdT negative adult patients had very low peripheral blast cell counts (less than 500/ul), which might have been caused by the insensitivity of the assay for very small numbers of TdT positive cells. (17 Refs)

7. ENZYMATIC PROPERTIES IN PERICELLULAR MEMBRANES OF LEUKEMIC CELLS.

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Adv Exp Med Biol; 145:377-384 1982

Enzyme characteristics of the plasma membrane were analyzed biochemically in cell populations isolated from the peripheral blood of leukemic patients to distinguish the various types of acute leukemias. Very low enzyme activities were generally recorded in cells of both non B/non T lymphoblastic and T leukemias. Differences in the activity of some enzymes were sufficient to allow a clear-cut differentiation of the two leukemic cell populations. In lymphoblastic leukemia high 5'-nucleotidase activity was measured with a mean level of approx 45 nanomole (nmol)/hr/10(6) cells. In some patients, the activity reached a mean value of 230 nmol/hr/10(6) cells, suggesting an earlier differentiation stage of the corresponding leukemic cells. Compared to the control mononuclear cell population, moderate decreased activities were measured for 5'-nucleotidase, alkaline phosphomonoesterase, and gamma-glutamyltranspeptidase. The activity of 5'-phosphodiesterase was significantly high in approx 40% of the patients while in the remainder it was practically undetectable or very low (range 0-2.5 nmol/hr/10(6) cells). The absence of activity of 5'-phosphodiesterase was inversely related to the expression of the immune associated antigen (Ia), whereas the absence of Ia correlated with the presence of high activity (range 3.8-16.8 nmol/hr/10(6) cells). A positive low level of terminal deoxynucleotidyl transferase activity was observed in approx 20% of patients but with an activity range (0-30 picomole/min/mg protein) and distribution similar for both subgroups of acute myeloid leukemia. (14 Refs)

8. ACID HYDROLASES AS MARKERS OF MATURATION IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA.

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Blood; 60(1):220-227 1982

Malignant lymphocytes from 30 B-cell chronic lymphocytic leukemia (B-CLL) patients were studied for the cytochemical localization of two acid hydrolases, alpha-naphthyl acetate esterase (ANAE) and acid phosphatase (AT). The large majority of the cells stained for both ANAE and AP in 7 cases, for AP only in 18 cases, and were negative for both the enzymes in 5 cases. Ultrastructural analysis revealed that the cells that displayed more mature morphological features, such as well developed smooth and rough membrane compartments, were those positive for acid hydrolases. The ANAE and AP are expressed by B cells at late stage of maturation was confirmed by the finding that some lymphocytes and all of the plasmacytoid lymphocytes and plasma cells from Walderstrom's macroglobulinemia, from mixed cryoglobulinemia, and from multiple myeloma patients stained strongly for both ANAE and AP. Using the expression of acid hydrolases and certain ultrastructural features as markers of cell differentiation, it was possible to demonstrate a process of maturation within the single B-CLL clones with accumulation of the cells at stages that differed in the various cases. (Author abstract) (37 Refs)

9. RIBONUCLEASE DEFICIENCY IN LYMPHOCYTES OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL).

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Dept. Biomedical Diagnostics, Medical Acad. Krakow, Krakow, Poland
Folia Haematol (Leipz); 109(2):201-212 1982

Ribonuclease (RNase) activity in the lymphocytes of 20 chronic lymphocytic leukemia (CLL) patients and 10 normal subjects was studied. It was found that in the lymphocytes of the control subjects the RNase activity could be detected in the pH range 4.5 to 8.6, inclusive. The RNase activity versus pH profile of normal lymphocytes consists of an acid RNase peak at pH 6.5 and alkaline RNase peak at pH 7.8. When treated with pCMB an inhibitor-bound RNase activity was revealed. The peak of this activity lay between pH 6.7 to 7.0. Liberating the inhibitor-bound RNase activity changed the RNase activity-pH profile, yielding one peak curve with a max at pH 7.0. RNase activity in CLL lymphocytes was remarkably lower than that in normal lymphocytes. The acid RNase in 80% of the CLL patients was lower by a factor of 10. Likewise, a many fold decrease in alkaline RNase activity (in some cases down to the zero level) was observed in CLL lymphocytes. However, in 70% of CLL patients, a level of the inhibitor-bound RNase activity was similar to that found in normal lymphocytes. In 20% of the studied CLL patients, a remarkable decrease in both free alkaline and inhibitor-bound RNase activity was observed. When poly-D was used as a substrate for determining RNase activity, a decrease to approx 15% in CLL lymphocytes was observed, when poly-U was used instead of poly-C, a decrease to 65% was found only as compared with normal lymphocytes. This may suggest that CLL lymphocytes are deficient in a poly-C specific RNase which displays its activity within a neutral and alkaline pH range. (Author abstract) (19 Refs)

10. INTRACELLULAR ZINC IN CHRONIC LYMPHOCYTIC LEUKEMIA.

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Clin Immunol Immunopathol; 24(1):26-32 1982

In this study, we measured the intracellular zinc (Zn) concentration of normal blood lymphocytes and of B-cell chronic lymphocytic leukemia (CLL) lymphocytes using anodic stripping voltometry analysis of Ficoll-Hypaque-isolated cells. A significant difference was found between the mean Zn concentration of normal lymphocytes (10.1 +-0.8 ng/10(6) cells) and those from patients with CLL (4.3 +-0.4 ng) (p less than 0.01). Patients with late-stage CLL had significantly less intracellular lymphocyte Zn (ng/10(6) cells) than did early stage patients, 3.5 +-0.4 and 5.8 +-0.8, respectively (p less than 0.05). Overall, in the total patient populations, there was a significant inverse correlation between the absolute peripheral blood lymphocytosis and Zn concentration/10(6) cells. Concentration of Zn in serum was within the normal range among all patients. There was no correlation between lymphocyte Zn levels and proportion of B- and T-lymphocyte subpopulations. Exogenous Zn did not amplify mitogen response of lymphocytes. The implications of these findings in lymphocyte function in CLL are discussed. (Author abstract) (14 Refs)

11. ECTOPICALLY PRODUCED CALCITONIN IN HUMAN HEMOBLASTOSES.

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Klin Wochenschr; 60(13):667-672 1982

The incidence of elevated serum levels of immunoreactive calcitonin (CT) in human myeloproliferative and lymphoproliferative disorders was investigated. On the basis of twice the normal range, about 45% of patients with acute leukemia and blast crisis of chronic myelocytic leukemia (CML) showed elevated serum levels of CT. Markedly elevated levels (greater than 1,000 pg/ml) were only found in this group. Since immunoreactive CT dropped to normal or only slightly elevated levels in remission and increased again before or during relapse, serum CT levels seem to reflect the activity of the disease. However, in patients with chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma, a lower incidence and only slightly elevated serum values were found. In addition, the mol wt of the proteohormone in serum specimen and cell extracts was investigated by gel chromatography. Besides physiological CT, different high-mol wt forms of the hormone could be demonstrated in serum and in cell extracts. Extracts of leukemic cells revealed higher molecular forms only. It is suggested that the proteohormone is ectopically produced by leukemic cells. (Author abstract) (27 Refs)

12. TOTAL AND SURFACE-LOCATED SIALIC ACID LEVELS IN NORMAL AND LEUKEMIC LYMPHOCYTES: RELATIONSHIP TO T AND B CELL NATURE AND TO LOCATION IN VIVO.

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Eur J Cancer Clin Oncol; 18(5):437-446 1982

Unfractionated normal blood lymphocytes (predominantly T lymphocytes) showed significantly elevated total and neuraminidase-susceptible sialic acid compared with CLL lymphocytes (predominantly B lymphocytes). T-enriched fractions from normal blood contained about three-fold the sialic acid content of the corresponding T-depleted fractions, and similarly low values were also obtained for T-depleted fractions from tonsils. Thus the reduced sialic acid levels in CLL lymphocytes appear to be due to their B cell nature. In contrast to the situation in normal peripheral venous blood, tonsillar T and B cells did not differ markedly in sialic acid content, suggesting that for T cells maturity and/or location in vivo are important determinants of this parameter. Results with calf thymocytes were in agreement with this. Sialic acid was estimated in malignant B and T lymphoblasts. Shedding of sialic acid-containing moieties from lymphocytes was also examined. (Author abstract) (50 Refs)

13. PRETREATMENT PROGNOSTIC FACTORS AND HOSPITALIZATION PERIODS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

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Isr J Med Sci; 18(4):447-455 1982

Pretreatment prognostic factors and hospitalization periods were analyzed in 57 consecutive children who had acute lymphoblastic leukemia diagnosed between 1967 and 1977, and who were followed up for at least 2 yr. We investigated possible correlations between white blood cell (WBC) count, organomegaly and mediastinal enlargement at diagnosis, as well as age and sex, with the length of first remission and survival. Children presenting with a combination of all of the following four risk factors - WBC count greater than or equal to 50,000/mm3, enlarged mediastinum, spleen and liver greater than or equal to 3 cm below the costal margin - comprised a poor-prognosis group, in which boys predominated. Age in this small group of patients had no correlation with prognosis. On the other hand, no specific risk factor was predictive for survival in the 48 children who had less than four of the risk factors. In this better-prognosis group, children less than 2 yr and greater than 10 yr had a higher relapse rate than those of intermediate ages, and girls had a significantly better prognosis than boys, These results indicate that age and sex are intercorrelated with the above risk factors, so that analysis of the effect of a single risk factor or even a combination of two factors can be misleading. In the light of these findings, an interpretation of the discrepancies in the literature is suggested. Of interest, too, is the poor prognosis and the high frequency of T-cell leukemia among Arab children. Finally, we stress the importance of day-care facilities that enable shorter hospitalization periods and improve the quality of life. (Author abstract) (26 Refs)

14. A PROGNOSTIC FACTOR ANALYSIS FOR USE IN DEVELOPMENT OF PREDICTIVE MODELS FOR RESPONSE IN ADULT ACUTE LEUKEMIA.

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Cancer; 50(3):457-465 1982

The pretreatment characteristics of 325 adults with acute leukemia who were treated at the M D Anderson Hospital between 1973 and 1977 have been evaluated to assess their value as prognostic indicators. The patient population includes all patients treated with an anthracycline (Adriamycin or rubidazone), cytosine arabinoside, vincristine, and prednisone during the time period. Most patients had one of the variants of acute

myelogenous leukemia (75%), and the remaining patients had acute lymphoblastic leukemia (16%) or undifferentiated leukemia (8%). Twenty-one factors were found to be significantly associated with probability of obtaining a complete response. In addition to characteristics previously known to provide prognostic information such as age, temperature status at the start of treatment, morphology, the presence of Auer rods, sex, and hemoglobin level, we identified the presence of a documented antecedent hematologic disorder and the finding of insufficient metaphases on cytogenetic analysis using the squash technique as being major prognostic variables. In addition, the pretreatment biochemical characteristics of hypoalbuminemia and elevated blood urea nitrogen and creatinine were found to adversely influence prognosis. The prognostic significance of factors such as the leukocyte count and platelet count, identified in earlier studies, was not confirmed in this group of patients. From this natural-history analysis predictive models for response have been developed using multivariate logistic regression techniques. One of these models has been used to evaluate the effect of morphology, treatment, and cytogenetic pattern on response to the combination of drugs used. (Author abstract) (24 Refs)

15. REDUCED T-COLONY FORMING CAPACITY IN B-CHRONIC LYMPHOCYTIC LEUKAEMIA. II. CORRELATION WITH CLINICAL STAGE AND FINDINGS IN B-PROLYMPHOCYTIC LEUKAEMIA.

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Leuk Res; 6(3):329-333 1982

T-colony growing capacity of samples obtained from 33 patients with B-cell chronic lymphocytic leukemia (B-CLL) and 5 with B-cell chronic prolymphocytic leukemia (B-PLL) was studied to investigate the correlation with Rai's clinical staging and the proportion of circulating T-lymphocytes with suppressor phenotype (T-gamma). All patients were untreated or had been off therapy for at least 5 mo. According to Rai's staging, 9 B-CLL patients had Stage 0 disease, 8 Stage I, 14 Stage II, and 2 Stages III-IV. The overall proportion of T-gamma cells was significantly increased in both B-CLL and B-PLL compared with normal controls. The proportion of T-lymphocytes with helper phenotype (T-u) was significantly reduced in both diseases. In B-CLL the mean number of T-colonies (mean 31 +-32.5) was significantly lower than with normal T-lymphocytes (mean 121 +-36.1). T-colony forming capacity was related to the clinical stage of the disease. Seven of the 9 Stage 0 samples gave rise to more than 50 colonies (77.7%), while only 5/24 Stages I-IV samples (20.9%) gave the same number of colonies. In four of the five B-PLL tested, the T-colony growth of the purified T-lymphocytes was markedly reduced. The T-colony numbers and the percentage of T-gamma cells were correlated in 26 patients with B-CLL and B-PLL. Results indicated that the T-colony forming capacity appears correlated to disease progression. (13 Refs)

16. CLINICOPATHOLOGICAL SUBTYPES IN HAIRY-CELL LEUKEMIA.

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Am J Clin Pathol; 78(1):80-85 1982

Thirty-six patients with hairy-cell leukemia (HCL) were evaluated, and were divided in two major subtypes: leukopenic (WBC less than 3,000/ul) and non-leukopenia (WBC greater than 3,000/ul). There were 22 leukopenic and 14 non-leukopenic patients. The leukopenic group were older than the non-leukopenic group, with an average age of 58.4 years compared with 47.6 years. The male/female ratio was higher in the leukopenic (6.3) than the non-leukopenic (2.0) patients. Splenomegaly, hepatomegaly and lymphadenopathy were found in 66%, 32%, and 18% of the leukopenic patients, compared with 92%, 57%, and 35% in the non-leukopenic patients. The leukopenic HCL was associated with more severe anemia, granulocytopenia, monocytopenia, and thrombocytopenia, and higher incidence of serious infections than the non-leukopenic HCL. Increased bone marrow reticulin fibers and unsuccessful marrow aspirations (dry taps) were more frequently associated with the leukopenic than the non-leukopenic HCL. (Author abstract) (27 Refs)

17. BASOPHIL PRODUCTION IN MYELOPROLIFERATIVE DISORDERS: INCREASES DURING ACUTE BLASTIC TRANSFORMATION OF CHRONIC MYELOID LEUKEMIA.

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Blood; 60(1):113-120 1982

We have examined basophil production (BP) in suspension cultures of separated peripheral blood cells from patients with chronic myeloid leukemia (CML). Seventy cultures were performed in 47 patients, 33 in chronic and 14 in the accelerated/acute phase of CML. None of 13 normal controls, 0/21 treated chronic phase, 3/33 untreated chronic phase, and 14/18 (p less than 0.0001) acceleraied/acute phase CML cultures showed at least twofold increases in basophils and histamine in vitro at 14-21 days. A gradient effect of disease phase on BP was observed: maximal histamine content (ng/10(6) cells) was 16 +-4 for chronic, 56 +-19 for accelerated, and 183 +-73 for acute phase CML cultures (mean +- SE, p less than 0.002), while basophils (per 10(3) cells) numbered 23 +-7, 59 +-20 and 267 +-81, (mean +- SE, p less than 0.0003), respectively. Multivariate analysis of maximal differences in basophils or histamine in vitro and simple linear regression slopes of basophils or histamine on time revealed that disease phase, and not therapy, accounted for the changes in BP in vitro. Serial studies over periods of 6-29 mo in four patients followed from chronic through acute phases of disease revealed a reversal of BP in vitro from negative to positive in four/four, with death supervening within 3 mo of study in three cases and refractory leukemia developing in the other. Whole blood histamine values were highest in untreated chronic phase CML (1,599 +-306 ng/ml, mean +- SE), while accelerated/acute phase values were comparable to treated chronic phase (513 +-131 and 521 +-101 ng/ml, respectively). Whole blood histamine and BP in CML relate closely to impending acute blastic transformation. The potential role of basophils and histamine in myelopoiesis and acute leukemic transformation of CML is discussed. (Author abstract) (26 Refs)

18. ACUTE NONLYMPHOCYTIC LEUKEMIA WITH BASOPHILIC DIFFERENTIATION.

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Blood; 60(1):38-45 1982

Four cases of acute nonlymphocytic leukemia with primitive basophilic differentiation are presented. In all four cases, study revealed Philadelphia chromosome negativity, and in none

were there clinical findings of chronic granulocytic leukemia. In each case, the leukemic blasts contained granules that failed to stain for peroxidase content but stained positively with toluidine blue. The former result could have led to the misclassification of the cases as lymphoid leukemias. Three of the four patients had physical findings that may have been due to circulating histamine excess. The histochemical and clinical features of these cases suggest that certain examples of leukemia with basophilic differentiation represent a distinctive variant of acute nonlymphocytic leukemia. (Author abstract) (35 Refs)

19. LEUKEMIC OPTIC NEUROPATHY.

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Ophthalmologica; 185(1):37-43 1982

Seven cases of leukemic ophthalmopathy were clinicopathologically studied. The present findings were as follows: (1) ocular manifestations were exactly parallel with the involvement of the central nervous system, (2) visual disturbance seemed to be caused mainly by neoplastic infiltration into the parenchyma of the optic nerve, compression of nerve fibers due to neoplastic invasion in the septal tissues, and vascular disturbance, and (3) the mechanism of papilledema or disc swelling might be chiefly attributed to neoplastic infiltration into the optic nerve and/or the central nervous system. (Author abstract) (16 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

20. SEROLOGICAL ANALYSIS OF CELL SURFACE ANTIGENS OF NULL CELL ACUTE LYMPHOCYTIC LEUKEMIA BY MOUSE MONOCLONAL ANTIBODIES.

Ueda R, Tanimoto M, Takahashi T, Ogata SI, Nishida K, Namikawa R, Nishizuka Y, Ota K
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Proc Natl Acad Sci USA; 79(14,part1):4386-4390 1982

Nine antigen systems were defined. Two were related to HLA-A,B,C and to Ia-like antigens; the others could be grouped into three categories. (i) NL-22, NL-1: NL-22 antibody reacted with leukemia cells from 12 of 16 cases of null cell acute lymphocytic leukemia (null-ALL) but not with any other type of leukemia tested or with lymphoid cells of various origins. Among cultured cell lines tested, one (NALM-6) of three null-ALL cell lines was positive; the others were negative. Absorption analysis confirmed the restriction of NL-22 antigen to null-ALL. NL-1 antibody was reactive with leukemia cells from 10 of 16 cases of null-ALL and 3 of 6 cases of chronic myelocytic leukemia in blastic crisis (CML-BC). The antigen was present also on a minor population of normal lymphoid cells. The distribution and mol wt (100,000; glycoprotein) of the NL-1 antigen resembled that of the previously described common ALL antigen (cALL). (ii) NL-30, NL-4: Both antibodies exhibited almost identical patterns of reactivities against cultured cell lines tested. They reacted with leukemia cells from some cases of null-ALL, adult T-cell leukemia, and CML-BC, although they showed discordance in their reactivities against a panel of leukemia cells. (iii) NL-9, NL-8, NL-25: These three antibodies detect serologically distinguishable determinants on a broad range of leukemias and normal lymphoid and hematopoietic cell types. The antibodies analyzed in this study provide evidence for the heterogeneity of null-ALL by demonstrating a variety of antigen phenotypes on leukemia cells. One of the antigens (NL-22) appears to be restricted to null-ALL. (Author abstract) (27 Refs)

21. SURFACE IA-LIKE EXPRESSION AND MLR-STIMULATING CAPACITY OF HUMAN LEUKEMIC MYELOBLASTS: IMPLICATIONS FOR IMMUNOTHERAPY AND PROGNOSIS.

Miale TD, Stenke LA, Lindblom JB, Sjogren AM, Reizenstein PG, Uden AM, Lawson DL
Cook Children's Hosp., 1212 West Lancaster Ave., Fort Worth, TX, 76102
Acta Haematol (Basel); 68(1):3-13 1982

Surface Ia-positive cells were found to vary from 0 to 100% in initial blood specimens from 37 adults with acute myelogenous leukemia (AML). When myeloblasts from 19 patients were tested against panels of lymphocytes from 5 to 19 normal donors, mean stimulation indices ranged from 1 to 60. Some leukemic myeloblasts strongly stimulated most allogenic responder lymphocytes whereas others produced almost no stimulation. The addition of antibody against human Ia to 28 mixed leukocyte reaction (MLR) combinations resulted in significant inhibition (p less than 0.001) of 3H-thymidine incorporation. Testing of myeloblastic Ia may have clinical relevance because patients with greater than 50% Ia-positive myeloblasts had a significantly longer survival than patients with fewer Ia-positive myeloblasts (p less than 0.04). (Author abstract) (39 Refs)

22. ALLOANTIGEN-INDUCED SUPPRESSOR- AND MEMORY CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Kabelitz D, Fink U, Reichert A, Rastetter J
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Immunobiology; 161(5):457-463 1982

T cell function was evaluated in patients with B cell type of chronic lymphocytic leukemia (CLL). Unseparated peripheral blood lymphocytes (PBL) and T cells from CLL patients stimulated in a primary allogeneic MLR were able to inhibit significantly a second MLR between the original responder (CLL) and stimulator (normal PBL) cell donors. Furthermore, it is shown that T lymphocytes from patients with CLL develop immunologic memory during the course of a primary MLR as evidenced by an enhanced response in secondary MLR. These results are discussed with respect to recently described imbalances of T cell subpopulations in CLL. (Author abstract) (15 Refs)

23. THE IMMUNOLOGICAL CLASSIFICATION OF LEUKAEMIA BASED ON A RAPID MICROCYTOTOXICITY TEST.

Billing RJ, Foon KA, Linker-Israeli M
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Clin Exp Immunol; 49(1):142-148 1982

We describe a rapid, accurate, and reproducible cytotoxic antibody test for the immunological classification of leukemia. Well characterized heteroantisera and monoclonal antibodies were distributed in a microcytotoxicity tray referred to as a leukemia screening tray (LST). Leukemia cells were tested for the presence of Ia-like, 'blast', thymocyte, common acute lymphoblastic leukemia (cALL), and acute myeloblastic leukemia (AML) antigens. Utilizing this technique, T ALL could be dis-

tinguished from non-T ALL, ALL and AML could be differentiated, the myeloid blast crisis of chronic myelogenous leukemia (CML) could be distinguished from the lymphoid blast crisis, and the T lymphocyte and B lymphocyte lymphoid leukemias were readily identified. It has been shown that subclassification of leukemia according to surface markers, as described here, offers considerable improvement in the diagnosis and treatment of leukemia over the classical morphological methodologies. Because the test can be completed in 2 hr and unlimited amounts of monoclonal antibodies are available, the LST or similar tests should become universally available in the future to supplement morphological data and replace other lengthy enzyme and rosetting tests. (Author abstract) (34 Refs)

24. ISOLATION OF MYELOID PROGENITOR CELLS FROM PERIPHERAL BLOOD OF CHRONIC MYELOGENOUS LEUKEMIA PATIENTS.

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Blood; 60(1):30-37 1982

Myeloid progenitor cells (colony- and cluster-forming cells in semisolid medium, CFU-GM) were purified from the peripheral blood of chronic myelogenous leukemia (CML) patients. Lymphocytes, monocytes, and most immature myeloid cells were simultaneously depleted with specific monoclonal antibodies using an erythrocyte rosette technique for cell separation. Cells expressing Ia-like antigen were then selected from the residual cell population. Day 7 CFU-GM were enriched 44-116-fold in the Ia+ cell fraction, when compared to the unseparated cells, and up to 47% of the cells could form a myeloid colony or cluster in culture. This cell fraction contained up to 92% undifferentiated blasts, with the remainder mostly promyelocytes. The enriched CFU-GM cells were dependent on an exogenous supply of colony-stimulating factor for growth, and colony formation was linear with cell concentration over a large range (10(4) -10(1) cells/ml). This technique of rosette depletion and enrichment with specific monoclonal antibodies provides a unique method for purifying a homogenous population of myeloid precursor cells with defined surface antigen characteristics. (Author abstract) (50 Refs)

25. IMBALANCE OF T CELL SUBPOPULATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA OF THE B CELL TYPE.

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Clin Exp Immunol; 49(1):157-162 1982

T cell enriched mononuclear cells from the peripheral blood of 20 patients with histologically and immunologically defined chronic lymphocytic leukemia of the B cell type (B-CLL) and 20 healthy individuals of various ages were investigated with T cell-specific monoclonal antibodies (OKT 4 and OKT 8) with regard to their subpopulation distribution. In B-CLL, a significant increase of lymphocytes reacting with OKT 8 could be demonstrated. Whereas there was a ratio of OKT 4 to OKT 8 of 1.72 in the control group, and OKT 4 to OKT 8 ratio of 0.67 was found in the B-CLL as a whole. With increasing clinical stage in accordance with the Rai scheme, a further displacement of this ratio in favor of OKT 8 positive cells was found. These results clearly show that, in peripheral blood of patients with B-CLL, an abnormal distribution pattern of circulating T cell subpopulations is present and that this also has prognostic relevance. (Author abstract) (24 Refs)

26. TREATMENT OF LEUKEMIA AND LYMPHOMAS WITH INTERFERONS I. TREATMENT OF MYELOMAS WITH HUMAN INTERFERON B.

Miaset JL, Mathe G, Gastiaburu J, Goutner A, Dorval T, Gouveia J, Hayat M, Jasmin C, Schwarzenberg L, Machover D, Ribaud P, De-Vassal F, Horoszewicz JS
Service des Maladies Sanguines et Tumorales, Institut de Cancerologie et d'Immunogenetique, 12-16 avenue Paul-Vaillant-Couturier, 94800 Villejuif, France
Biomedicine; 36(1):55-59 1982

Eighteen patients with malignant gammopathies (16 with myeloma and 2 with Waldenstrom's disease) for a short time because in a Phase II-I trial were treated with human (IF beta) given iv 6 x 10(6) units weekly (7 patients) or 3 x 10(6) units twice weekly (11 patients) during at least 3 months if tolerated. Treatment was discontinued because of side-effects in three patients. Reduction of the M component of at least 25% from the initial value was obtained in three patients. In one case, was also observed the disappearance of a urinary Bence-Jones protein, in four cases a significant reduction of bone marrow infiltration by plasma cells and, in five cases, major alleviation or disappearance of bone pain. Length of treatment seems an important factor for activity. Immune monitoring with currently available tests, mainly NK cell activity, yielded no correlation with therapeutic effect in these patients. This very preliminary study demonstrates the effect of fibroblastic interferon in myeloma, but further studies are mandatory to determine the population of patients likely to benefit from treatment, the best modalities, possible special indication, dose schedule and duration of treatment. Interferon, however, already appears in this population of patients as giving results similar to those of single agent chemotherapy. As it is not myelosuppressive, it could be indicated in that frequent situation of advanced myeloma with bone marrow failure contraindicating combination chemotherapy. (Author abstract) (23 Refs) (In FRE)

CHEMOTHERAPY

27. TREATMENT OF RELAPSED ACUTE MYELOCYTIC LEUKEMIA WITH A COMBINATION OF ACLARUBICIN AND CYTOSINE ARABINOSIDE.

Takahashi I, Hara M, Uchida K, Takaoka K, Watanabe S, Lai M, Hamasaki K, Kohi F, Kitajima K, Kimura I, Adachi T, Yoritsu S, Tokioka M, Sanada H
Dept. Medicine, Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 36(1):77-80 1982

Relapses in nine patients with acute myelocytic leukemia were treated with a combination of aclarubicin (ACR) and cytosine arabinoside (ara-C). ACR, 40 mg/m2/day, was administered daily by intravenous injection from Day 1 to Day 3 and ara-C, 60-80 mg/m2/day, divided into two doses, was given every 12 hr by intravenous infusion from Day 1 to Day 7. Depending on the state of the bone marrow, ACR-ara-C regimen was modified in administration period and repeated after the resting periods of at least 7 days. Complete remission was obtained in seven of nine patients (77.8%). The time required for achieving the complete remission varied from 20 to 55 days with a median of 39 days. The duration of complete remission was from 8 to 52 weeks with a median of 22 weeks. Side effects on digestive system such as nausea, vomiting and anorexia, were seen in all patients, although they were managed by symptomatic treatment. The results indicate the effectiveness

of this ACR-ara-C regimen in the clinical management of acute nonlymphocytic leukemia. (Author abstract) (8 Refs)

28. CLINICAL PHARMACOLOGY OF 9-BETA-D-ARABINOFURANOSYLADENINE IN COMBINATION WITH 2'-DEOXYCOFORMYCIN.

Agarwal RP, Blatt J, Miser J, Sallan S, Lipton JM, Reaman GH, Holcenberg J, Popiack DG
Section Medical Oncology, Boston Univ. Medical Center, 75 E. Newton St., Boston, MA, 02118
Cancer Res; 42(9):3884-3886 1982

It has been suggested that, by inhibiting the adenosine deaminase (ADA)-mediated catabolism of 9-beta-D-arabinofuranosyladenine (ara-A), 2'-deoxycoformycin (DCF) would increase the half-life (t1/2) of ara-A, a compound with known antileukemic activity. To test this hypothesis, we collected serial plasma samples from five patients with refractory acute lymphoblastic leukemia who participated in a Phase I trial of iv DCF (15 mg/sq m) in combination with iv single-dose ara-A (120-250 mg/sq m). In four of these patients, of whom three were known to have achieved greater than 98% ADA inhibition, a mean ara-A t1/2 of 227 min was achieved. Extrapolated peak levels (ie, following infusion of Ara-A) ranged from 1.5 to 7.4 ug/ml (mean, 4.2 ug/ml). Elimination of drug appeared to follow a single-compartment model. In two patients who received ara-A without prior DCF and in a third patient who had significant residual ADA activity despite DCF, ara-A was unmeasurable within 5 min of the end of infusion. These data confirm that the kinetics of ara-A catabolism can be altered by inhibition of ADA and suggest that more than one dose of DCF may be necessary for complete inhibition of the enzyme and optimal pharmacological modulation of ara-A. (Author abstract) (13 Refs)

29. MENINGEAL LEUKEMIA FOLLOWING LYMPHOID BLAST CRISS IN CHRONIC MYELOID LEUKEMIA: THERAPEUTIC IMPLICATIONS.

Cazzola M, Nalli G, Brusamolino E, Dacco M, Ghizzi A, Molinari E, Tagliabue A
Patologia Medica 1, Policlinico S. Matteo, 27100 Pavia, Italy
Tumori; 68(3):257-263 1982

Five of 40 patients with chronic myeloid leukemia (CML) had lymphoid blast crisis and 4 of them achieved complete remission of metamorphosis with vincristine and prednisone. While in hematologic remission, two of these subjects developed meningeal leukemia. Clinical and biologic data indicated that the course of the disease after lymphoid blast crisis was very similar to that of acute lymphoblastic leukemia (ALL). It is suggested that patients with CML who develop lymphoid blast crisis should be treated with an intensive therapeutic protocol including early prevention of meningeal leukemia. (Author abstract) (20 Refs)

30. CHILDREN BORN OF PARENTS WITH LEUKEMIA. A REVIEW OF 23 CHILDREN.

Marradi P, Schaison G, Alby N, Berger R, Jacquillat C, Boiron M
Hopital Saint-Louis, 2, place du Docteur Fournier, F-75116 Paris, France
Nouv Rev Fr Hematol; 24(2):75-80 1982

Twelve children fathered by men who had acute lymphoblastic leukemias (ALL) were born normal and healthy following uncomplicated, term births. The psychomotor and physical development of these children paralleled the norms of their age groups, and the children showed no particular susceptibility to infections. Eight women with either acute myeloblastic leukemia (3) or ALL (5) gave birth to 11 children. One patient who was treated for ALL during 8.5 yr with prednisone and 6-mercaptopurine gave birth to a boy with multiple birth defects associated with hypopituitarism and a mid-line defect. Another patient who was treated for ALL with prednisone and vincristine for 6 yr gave birth to a boy with laparoschistasis. Two other patients gave birth to children with minor defects. One baby was retrognathic and had a hiatal hernia. The other child was a premature girl who had serious neonatal anoxia. The treatment which the mothers of malformed children received was similar to that of other mothers in the series. (54 Refs) (In FRE)

31. RELATIONSHIP OF THE DURATION OF THE CHRONIC PHASE IN CHRONIC GRANULOCYTIC LEUKEMIA TO THE NEED FOR TREATMENT DURING THE FIRST YEAR AFTER DIAGNOSIS.

Wareham NJ, Johnson SA, Goldman JM
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Cancer Chemother Pharmacol; 8(2):205-210 1982

The relationship between the duration of chronic phase in 25 patients with previously untreated chronic granulocytic leukemia (CGL) and the amount of busulfan administered during the first yr after diagnosis was investigated. The total dose of busulfan administered in the first yr after diagnosis ranged from 300-1,300 mg. The duration of chronic phase disease ranged from 13-72 mo. For 11 patients in whom chronic phase disease was relatively protracted, its duration ranged from 47-136 mo. The dose of busulfan administered to these patients during the first yr after diagnosis ranged from 0-300 mg. In the 25 patients in this study, busulfan dosage in the first yr after diagnosis was significantly related to the duration of their first chronic phase. Results indicate that patients requiring little or no treatment within the first yr after diagnosis have an excellent chance becoming long-term survivors. (17 Refs)

32. HYPERGONADOTROPIC HYPOGONADISM, SHBG DEFICIENCY AND HYPERPROLACTINAEMIA: A TRANSIENT PHENOMENON DURING INDUCTION CHEMOTHERAPY IN LEUKEMIC CHILDREN.

Beck W, Schwarz S, Heidemann PH, Jentsch E, Stubbe P, Konig A
Dept. Paediatics, Univ. Gottingen, Humboldtallee 38, D-3400 Gottingen, W. Germany
Eur J Pediatr; 138(3):216-220 1982

Hypothalamo-pituitary-gonadal function was evaluated in five pubertal boys (16-19 yr old) and four prepubertal girls with acute lymphoblastic leukemia before and during (day 10, 21 and 28) and 23 days after the induction phase of treatment with vincristine (VCR), daunorubicin (DAU), L-asparaginase (ASP), and prednisone (PR). After 3 wk of therapy, plasma testosterone and estradiol levels decreased while both boys and girls showed decreased binding capacity of sex-hormone-binding globulin. Testicular volume in boys also was decreased. At the same time basal luteinizing hormone (LH), follicle stimulating hormone, and prolactin values doubled with a normal gonadotropin response to LH releasing hormone. The prolactin response to thyrotropin-releasing hormone increased at the end of the induction phase, when treatment with VCR, DAU, and ASP were discontinued, while PR was continued for 7 days. All hormonal values, and testicular volume in boys, became normal within a period of 3 wk after induction therapy, despite continued therapy with other antileukemic agents and radio-

therapy. The mechanisms involved in these hormonal and gonadal changes are discussed. (35 Refs)

33. COLONY-FORMING ASSAY FOR CIRCULATING CHRONIC LYMPHOCYTIC LEUKEMIA CELLS.

Tuttle R, Richardson D, To D, Royston I, Mendelsohn J
Univ. Hosp. H720, 225 Dickinson St., San Diego, CA, 92103
Leuk Res; 6(3):335-344 1982

Adaptation of a technique for growth of B lymphocyte colonies to peripheral blood cells of 18 patients with clinically and pathologically typical chronic lymphocytic leukemia (CLL) is reported. T-lymphocyte-depleted CLL peripheral blood cells were cultured with irradiated, normal T cells, and media conditioned by normal, mitogen-stimulated T cells in methylcellulose. Small colonies of approx 40 cells appeared after 5-7 days incubation and little or no growth was noted in the absence of irradiated T lymphocytes. The relationship between the number of cells plated and number of colonies observed was linear over a wide range of plating concentrations. No correlation was observed between plating efficiency and the number of circulating leukocytes or lymphocytes. A high percentage of CLL colony-forming cells were synthesizing DNA (S phase). Cells harvested from normal T lymphocyte colonies were greater than 95% sheep red blood cell-rosette positive and greater than 95% positive when stained for OKT3 and/or T101, compared with less than 5% of cells harvested from CLL colonies. The presence of large numbers of surface immunoglobulin positive cells could not be demonstrated in CLL colonies. Drug sensitivity studies to adriamycin (ADM) and melphalan (ME) were performed on five patients previously treated with alkylating agents and five patients who were untreated. CLL colony-forming cells were relatively resistant to ADM, although untreated patients were less resistant than previously treated ones. Previously treated patients were also relatively resistant to ME. Results indicated that the reported system can be used to study regulation of CLL cell proliferation, and may have utility in predicting response to chemotherapeutic agents. (37 Refs)

34. CELL KINETICS IN ACUTE LEUKEMIA. A CRITICAL REEVALUATION BASED ON NEW DATA.

Hiddemann W, Buchner T, Andreeff M, Wormann B, Melamed MR, Clarkson BD
Medizinische Universitatsklinik, Westring 3, 4400 Munster, W. Germany
Cancer; 50(2):250-258 1982

The current study was undertaken to compare biopsy and aspiration sampling techniques for reliable cell kinetic analysis in acute leukemia and to reevaluate the clinical significance of cell kinetic data in this disease. Ad 1; One hundred forty-three paired simultaneously taken marrow aspirates and Jamshidi biopsies from 61 patients with acute nonlymphocytic leukemia (ANLL) were compared by means of flow cytometry (FCM) for cellular DNA and RNA measurements, autoradiography for 3H-TdR labeling index and liquid scintillation counting of 3H-TdR uptake. Aspirates were found unreliable for pretreatment evaluation and for monitoring of drug induced cell kinetic perturbations due to contamination with peripheral blood. Aspiration should, therefore, be replaced by marrow biopsy which provides reliable sampling of bone marrow for cell kinetic studies. Ad 2; FCM S-phase index determined from biopsy material was not found predictive for therapeutic response in 43 patients with ANLL treated with two different induction regimens. In one of the two protocols, changes in FCM S-phase index after 48 hr continuous infusion of cytosine arabinoside correlated significantly with response and nonresponse, respectively. (Author abstract) (67 Refs)

MULTIMODAL THERAPY

35. EFFECT OF THERAPY ON T CELL SUBPOPULATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Kay NE, Howe RB, Douglas SD
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Leuk Res; 6(3):345-348 1982

Fifteen chronic lymphocytic leukemia (CLL) patients were studied at various stages of the disease in order to delineate more closely the significance of imbalance in the T cell subsets in CLL. All patients studied were diagnosed as B cell type of CLL by clinical presentation and use of surface immunofluorescence staining procedures. The stage of each patient was determined by the Rai classification system. T cell studies were performed prior to chemotherapy or 3-4 wk post-therapy. An increase above control in the mean value of total T cells, a significant increase in Tgamma cells, and a pronounced decrease in CLL Tmu cells over control were observed. The early stage patients had lower numbers of Tgamma cells than advanced patients but were still significantly above the level in controls although one patient was in the control range. The in vitro appearance of Tmu cells for early patients was greater than that of advanced group, but only one patient was in the control range (control mean Tmu 2,010 +-195). Three advanced patients were studied immediately prior to and 7-10 days after splenectomy. All three patients demonstrated significant reductions from the pre-operative absolute Tgamma cell concentration. No change was noted in the ability to develop Tmu cells in vitro. In all three patients the removed spleens were diffusely involved with malignant lymphocytes. The decrease in the proportion of Tgamma cells after splenectomy and the increase in Tgamma cells in progressive disease post-splenectomy suggested that Tgamma cells may be an important determinant of the course of CLL. (16 Refs)

SUPPORTIVE CARE

36. BONE MARROW TRANSPLANTATION FOR APLASTIC ANEMIA AND ACUTE LEUKEMIA.

Schaefer UW, Schmidt CG, Ruther U, Schuning F, Becher R, Beyer JH, Hossfeld DK, Nowrousian MR, Ohl S, Wetter O, Bamberg M, Schmitt G, Bormann U, Scherer E, Haralambie E, Linzenmeier G, Grosse-Wilde H, Hierholzer E, Kuwert E, Henneberg KB, Luboldt W, Richter HJ, Leder LD, Hantschke D
Innere Klinik und Poliklinik, Universitatsklinikum, Hufelandstr. 55, 4300 Essen 1, W. Germany
Dtsch Med Wochenschr; 107(21):803-808 1982

Twenty-six bone marrow transplantations were performed at the West German Tumor Center at Essen between December 1975 and December 1981. Three patients had aplastic anemia, 23 acute leukemia. Of the leukemia patients 13 had a recurrence and 10 were in full remission at the time of the transplantation. Two of the patients with a recurrence received deep-frozen autologous marrow from the remission phase. One patient with aplastic anemia had an identical twin as donor, while

all other patients received allogeneic marrow from histocompatible family members. Eleven patients are still alive, all three of those with aplastic anemia, one of those with leukemia in a recurrence, and seven of those with acute leukemia in full remission. Two of the survivors have a chronic graft-host reaction, but the others are symptom-free, after an observation period of up to 4 yr. Main causes of death were leukemic recurrence (6), infection (5), and graft-host reaction (2). It would seem that at present bone marrow transplantation offers the best chance of a cure for severe aplastic anemia and acute leukemia in adults, but only if transplantation is undertaken early and not in the end-stage of the disease. (Author abstract) (11 Refs) (In GER)

37. ALLOGENEIC MARROW TRANSPLANTATION FOR ACUTE LEUKEMIA IN RELAPSE.

Badger C, Buckner CD, Thomas ED, Clift RA, Sanders JE, Stewart PS, Storb R, Sullivan KM, Shulman H, Flournoy N
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):383-387 1982

Experience in 75 patients (2-36 yr old, median 17 yr) with acute lymphoblastic leukemia (ALL) and 63 patients (1-55 yr old, median 23 yr) with acute non-lymphoblastic leukemia (ANL) in relapse treated with cyclophosphamide and total body irradiation with and without additional chemotherapeutic agents followed by allogeneic marrow transplantation is presented. Twelve patients (7 ANL, 5 ALL) died between days 3 and 20 without evidence of engraftment. One hundred and three of 132 patients who had marrow aspirations performed in the first 14 days had no blasts in the marrow. Actuarial analysis demonstrated a significant difference in the probability of non-leukemic death between patients with ALL and patients with ANL, 56 vs 72%, and this was a consequence of older patients with ANL having a high rate on non-leukemic death. Twenty-five percent of ANL patients and 45% of ALL patients died of leukemia. The differences in relapse rates for the various regimens were not significant when compared within diagnostic categories or for the population as a whole. There was a suggestion that the addition of daunorubicin prolonged time to relapse in ALL (median 104 days vs medians of 71-148 days for four other regimens), and patients with ALL treated with carmustine had a 33% probability of relapsing; however, these were not statistically significant differences. The actuarial probability of long-term survival ranged from 7-17%; no significant differences between any of the treatment groups or between ALL and ANL were observed. Seventeen patients survived between 3-9.5 yr after transplantation. (16 Refs)

38. ALLOGENEIC MARROW TRANSPLANTATION FOR ACUTE NON-LYMPHOBLASTIC LEUKEMIA IN RELAPSE USING FRACTIONATED TOTAL BODY IRRADIATION.

Buckner CD, Clift RA, Thomas ED, Sanders JE, Stewart PS, Storb R, Sullivan KM, Hackman R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):389-394 1982

Twenty-three patients (10-52 yr old) with acute non-lymphoblastic leukemia in relapse were treated with cyclophosphamide (60 mg/kg on days-10 and-9), fractionated total body irradiation (200 rad/day on day-5 and day 0), and allogeneic marrow transplantation. One patient died of infection on day 17 without evidence of engraftment; all other patients achieved engraftment. Eight patients relapsed between 30 and 619 days after transplantation and died of leukemia-related problems. Six of the 23 patients (26%) were alive and free of disease 756-1,306 days following transplantation. Seven of the 22 patients with sustained engraftment developed significant acute graft-vs-host disease (GVHD, Grade 2 or greater). Eight of 15 patients surviving greater than 100 days developed chronic GVHD. Of 11 with sustained engraftment and no significant GVHD, none survived. Sixteen patients had cytogenetic studies of marrow prior to transplantation to detect leukemia-associated chromosomal abnormalities. In 2 patients such abnormalities could not be detected, and a variety of chromosomal rearrangements was present in the 14 other patients. All eight patients who relapsed after transplantation had leukemia-associated chromosomal markers before transplantation, and four of the patients had donors of opposite sex. After relapse, five patients were studied, and in all patients the recurrent leukemia cells were of host type. (23 Refs)

39. ALLOGENEIC MARROW TRANSPLANTATION FOR PATIENTS WITH ACUTE NON-LYMPHOBLASTIC LEUKEMIA IN SECOND REMISSION.

Buckner CD, Clift RA, Thomas ED, Sanders JE, Hackman R, Stewart PS, Storb R, Sullivan KM
Fred Hutchinson Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):395-399 1982

Results of allogeneic marrow transplantation in 24 patients (3-30 yr old) with acute non-lymphoblastic leukemia in second remission prepared with fractionated or single-dose total body irradiation (TBI) are presented. The first 7 patients were treated with 1,000 rad TBI in single dose, and the last 17 consecutive patients were randomized to receive either 1,000 rad TBI in a single dose (7 patients) or 1,200 rad of TBI fractionated over 6 days (10). All patients received 60 mg/kg cyclophosphamide on each of 2 successive days 3-5 days prior to the initiation of TBI. Twelve of the 24 patients died between day 17 and day 301 of causes unrelated to leukemia. Five patients died with severe graft-vs-host disease (GVHD) associated with infectious or hepatic complications. Five patients had a recurrent leukemia, four of whom died of leukemia-related problems. One patient was alive following an isolated relapse in the femur 746 days after transplantation. Seven patients were alive and disease-free 115-1,909 days (median 786 days) after transplantation. Of 12 patients with significant (Grade 2-4 acute and/or chronic) GVHD, 4 were alive without relapse 115-1,203 post-transplant. Of 12 patients with no significant GVHD (less than Grade 2 and no chronic), 3 were alive without relapse, 1 with relapse. Of the seven patients randomized to receive a single 1,000 rad TBI dose, three were alive 115, 187, and 544 days following transplantation. One of 10 patients randomized to receive 1,200 rad fractionated TBI was alive without relapse, and 1 was alive with relapse. Three of the first seven patients treated with 1,000 rad single dose TBI were alive 1,203, 1,522, and 1,909 days following transplantation. Results did not demonstrate an advantage to transplantation in second remission compared with transplantation in relapse. (18 Refs)

40. ALLOGENEIC MARROW TRANSPLANTATION USING FRACTIONATED TOTAL BODY IRRADIATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN RELAPSE.

Clift RA, Buckner CD, Thomas ED, Sanders JE, Stewart PS, Sullivan KM, McGuffin R, Hersman J, Sale GE, Storb R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):401-407 1982

Results of treating 41 patients with acute lymphoblastic leukemia (ALL) in relapse with high dose cyclophosphamide (120 mg.kg) and fractionated total body irradiation (TBI) regimens (1,200-1,750 rad) followed by marrow transplantation from HLA-matched siblings are described. Six fractionated TBI regimens were evaluated. Forty of 41 patients had evidence of engraftment as determined by rising peripheral blood counts and histological examination of marrow. Ten patients died of non-leukemic causes between days 11 and 143 and had no evidence of residual or recurrent leukemia. Eighteen of 41 patients had radiographic evidence of pneumonitis. Clinically, 13/18 patients were thought to be interstitial, 4/18 alveolar, and 1/18 both alveolar and interstitial. Nine patients underwent open-lung biopsy. Ten of the 18 patients with pneumonitis died and the pneumonitis was the primary cause of death in 7 (1 histoplasmosis, 4 cytomegalovirus, 1 Pneumocystis, and 1 Candida). Ten patients died without evidence of leukemia, 9 during the first 66 days and 1 on day 143. One patient died on day 19 of infection but had persistent leukemia at autopsy. Of the 40 patients achieving sustained engraftment, 6 developed significant acute graft-vs-host disease (GVHD; Grade 2-4) and 7 developed chronic GVHD. Twenty-eight patients had neither significant acute or chronic GVHD, and 20/28 patients had leukemic relapse including 4 at extramedullary sites. Fourteen of the 27 patients who relapsed had donors of opposite sex; in 10/14 patients the chromosome marker on the leukemic cells was of host origin, and in 1/14 the origin could not be established. (27 Refs)

41. ALLOGENEIC MARROW TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN REMISSION USING FRACTIONATED TOTAL BODY IRRADIATION.

Clift RA, Buckner CD, Thomas ED, Sanders JE, Stewart PS, McGuffin R, Hersman J, Sullivan KM, Sale GE, Storb R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):409-412 1982

Twelve patients (4-29 yr old) with acute lymphoblastic leukemia (ALL) in second to fourth remission were treated with cyclophosphamide (120 mg/kg), 1,400 rad of fractionated total body irradiation, then allogeneic marrow transplantation. All patients were given methotrexate (MTX) 15 mg/square meter (m2) on day 1, 10 mg/m2 on days 3, 6, and 11, and then weekly to day 102 to prevent graft-vs-host disease (GVHD). Alternate MTX doses were given as 12 mg intrathecally from days 32 to 102 to prevent CNS relapse. Two of five patients transplanted in second remission had the initial relapse after maintenance chemotherapy had been discontinued. All patients achieved engraftment. Two patients died on days 32 and 62 of interstitial pneumonitis associated with cytomegalovirus. Six patients relapsed between day 59 and 659, and 4/6 died of leukemia-related problems. Two patients who relapsed were alive, one in relapse, and one in remission following local irradiation for isolated testicular relapse. Four patients were alive and free of disease from 658-992 days following transplantation. Eight patients did not have significant (Grade 2 or greater acute and/or chronic) GVHD: two died on days 32 and 62 of interstitial pneumonitis, five relapsed (1 survived), and one was alive and disease-free 838 days after transplant. All four patients with significant acute or chronic GVHD were alive. Results suggested that 1,400 rad fractionated irradiation is not more effective than 1,000 rad delivered in a single exposure in patients transplanted for ALL in remission or relapse either in terms of survival or of frequency of relapse. (23 Refs)

42. AUTOLOGOUS BONE-MARROW TRANSPLANTATION IN CALLA-POSITIVE ACUTE LYMPHOBLASTIC LEUKAEMIA AFTER IN-VITRO TREATMENT WITH J5 MONOCLONAL ANTIBODY AND COMPLEMENT.

Ritz J, Bast RC, Clavell LA, Hercend T, Sallan SE, Lipton JM, Feeney M, Nathan DG, Schlossman SF
Div. Tumor Immunology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Lancet; 2(8289):60-63 1982

A monoclonal antibody (J5) specific for the common acute-lymphoblastic-leukemia antigen (CALLA) was used for in-vitro pre-treatment of bone-marrow before autologous transplantation in four patients with CALLA positive acute lymphoblastic leukemia (ALL) in relapse, who did not have HLA-compatible donors. After remission induction and intensification, bone-marrow cells were harvested, treated with J5 antibody and rabbit complement, and cryopreserved in liquid nitrogen. Patients received ablative chemotherapy and total-body irradiation before reinfusion of autologous J5-treated bone marrow. The transplantation protocol was well tolerated, and engraftment of normal myeloid cells occurred in all four patients. Two patients have continued in unmaintained remission with complete hematopoietic reconstruction for more that 1 yr after autologous transplantation. (Author abstract) (23 Refs)

43. CYCLOSPORIN A AS PROPHYLAXIS AGAINST GRAFT-VERSUS-HOST DISEASE IN 36 PATIENTS.

Barrett AJ, Kendra JR, Lucas CF, Joss DV, Joshi R, Pendharkar P, Hugh-Jones K
Westminster Bone Marrow Transplant Team, Westminster Medical Sch., Children's Hosp., London, England
Br Med J; 285(6336):162-166 1982

Oral cyclosporin A was used as prophylaxis against graft-versus-host disease in (a) 31 patients with acute leukemia or aplastic anemia given transplants of HLA-matched bone marrow and (b) five patients with inborn errors of metabolism given transplants of haplotype-identical (parental) bone marrow. Twenty-six patients survived longer than 2 months after the operation. Despite the cyclosporin A, 31 patients (86%) suffered an acute form of graft-versus-host disease and 22 (61%) a chronic form. Nevertheless, the disease was usually treatable with immunosuppressive agents and caused the death of only one patient. Cyclosporin A caused renal toxicity in all cases; occasionally this was associated with a 'capillary leak' syndrome, fatal in two patients. In children hypertension, fits, and fluid retention were common side effects. Blood concentrations of cyclosporin A correlated with blood urea values and blood pressure but did not predict the occurrence of graft-versus-host disease. Four different dose schedules were used to find the optimum way to administer the drug. Oral cyclosporin A is extremely effective at reducing the severity of graft-versus-host disease, but prevention of the disease is limited by toxicity of the drug and variable absorption. Better results might be achieved with parenteral administration or by using the drug in combination with other methods. (Author abstract) (15 Refs)

44. CENTRAL VENOUS CATHETER IN THE TREATMENT OF ACUTE LEUKEMIA: INTRODUCTION OF A MODIFICATION OF THE HICKMAN TECHNIQUE.

Kubel M, Emmrich K, Helbig W, Schultze W, Ezold R, Dellemann K, Schwenke H
Medizinische Klinik, Karl-Marx-Universitat, Johannisallee 32, DDR-7010 Leipzig, E. Germany
Z Gesamte Inn Med; 37(8):245-248 1982

Central venous catheters were implanted by a modified Hickman technique in 34 patients with acute leukemia. Results were compared with those obtained with 63 cubital vein catheters in 30 patients. The catheterization allowed aggressive supportive measures, including cytostatic therapy, long-term infusions, transfusions, parenteral nutrition, and repeated blood sampling. The modified technique was recommended as an improvement over conventional techniques. (6 Refs) (In GER)

45. APPLICATION OF A LIVE VARICELLA VACCINE IN CHILDREN WITH ACUTE LEUKEMIA.

Sakurai M, Ihara T, Ito M, Hirai S, Iwasa T, Oitani K, Kamiya H, Izawa T, Takahashi M
Dept. Pediatrics, Mie Univ., Sch. Medicine, Tsu-city, Mie-ken, Japan
Excerpta Med Int Congr Ser; 571:87-93 1982

Forty-three children with acute leukemia who were susceptible to herpes virus and who had been vaccinated with Takahashi's live attenuated varicella zoster virus, were followed closely for 6 yr. Patients were vaccinated usually 6 mo after complete remission, when the immunological status of the patient had returned to normal. Clinical manifestations (fever and/or rash) developed in seven children but were only serious in one patient. After exposure to natural varicella infection on 31 possible occasions, only one patient developed an infection. The occurrence of herpes zoster infection was not significantly different from that in children who had natural varicella infection before onset of leukemia. It is concluded that a live attenuated varicella virus vaccine can be used in leukemic children in remission, and provides a potent measure for preventing natural varicella infection. (5 Refs)

CASE REPORTS

46. HEMOLYTIC ANEMIA BY AUTOANTIBODIES DURING CHRONIC LYMPHOID LEUKEMIA.

Zittoun R, Rio B, Rosenbaum J, Maury J, Dreyfus B, Clauvel J, Piette J, Leporrier M, Rochant H, Vernant J, Tobelem G, Zittoun R
Hopital Henri-Mondor, 51, avenue du Marechal-de-Lattre-de-Tassigny, F-94010 Creteil, France
Nouv Rev Fr Hematol; 24(2):89-94 1982

A case of autoimmune hemolytic anemia associated with chronic lymphoid leukemia (CLL) in a 72-yr-old man is presented. The patient presented with acute anemia and hyperlymphocytosis. The patient received several blood transfusions during his first hospitalizations. Subsequent hospitalizations revealed the presence of cytomegalovirus with erythroblastic hyperplasia and pathological nodular lymphoid infiltration revealed by medullary biopsy. Corticotherapy, antibiotics, and further transfusions were necessary. Heparine therapy was unable to modify the effects of a pulmonary embolism which led to the patients death. Alternative treatment approaches to the case include plasma exchanges if, within 48 hr, a double therapeutic approach of transfusions and corticosteroids is ineffectual in raising the hematocrit above 25%. Splenectomy is suggested for cases in which corticosteroids are contraindicated or ineffectual. The association of pulmonary embolisms and idiopathic autoimmune hemolytic anemia suggests disseminated lupus erythematosis or a related syndrome. Chemotherapy might have been immediately associated with the patient's therapy once a diagnosis of CLL was established. (11 Refs) (In FRE)

47. CARDIOVASCULAR TOXIC EFFECTS OF VM26 IN THE TREATMENT OF ACUTE LYMPHATIC LEUKEMIA. PRESENTATION OF TWO CASES.

Razon-Veronesi S
Divisone Pediatrica, Ospedale S. Carlo Borromeo, Via Pio II, 20135 Milano, Italy
Tumori; 68(3):253-255 1982

Two cases of acute lymphatic leukemia treated with VM26 underwent a severe cardiovascular syndrome with hypertension and cardiac failure. The first patient, 1 9-yr-old boy, after the appearance of hypertension suffered from serious cerebral hemorrhages which were lethal. The second patient, a 12-yr-old boy, also developed hypertension with retinal hemorrhages and cardiac failure. Hypertension was, however, controlled, the patient recovered, and at present he is in remission. Although cardiovascular toxic effects are not frequent after administration of VM 26, they should be known to the medical oncologist so that treatment of this side effect may be introduced at the first appearance of the symptoms. (Author abstract) (22 Refs)

48. ACUTE LEUKEMIA IN PREGNANCY. CLINICAL PROBLEMS AND DESCRIPTION OF FOUR CASES.

Bolis PF, Franchi M, Salvaneschi L
Instituto Clinica Ostetrica e Ginecologica, Universita di Pavia, Pavia, Italy
Minerva Ginecol; 34(5):347-353 1982

Four cases of acute leukemia (2 myloblastic, 1 lymphoblastic and 1 promyelocytic; pregnant women 22-31 yr old), were examined. In two cases abortions were induced after 17 and 25 weeks. Complete remission in these patients lasted 19 months and survival rates were 32 and 23 months, respectively. One patient spontaneously aborted at 9 weeks experienced complete remission for 3 months and survived 5 more. The fourth woman, diagnosed post-partum, gave birth at 36 weeks. She underwent complete remission for 21 months, surviving a total of 25. The necessity of using common antileukemic therapeutic practices with pregnant patients involves a risk to the fetus which increases until the completion of the 20th week. In more advanced pregnancies maternal exacerbation can lead to caesarean section which then increases maternal risk. In the case of fetal death continuing the pregnancy could create grave infective-hemorrhagic complication. It was concluded that interruption of the gestation permitted normal therapeutic practices and was obtained complete remission in two patients, while the same treatments during pregnancy would have exposed both mother and fetus to greater risks. (58 Refs) (In ITA)

49. PELVIC AND OVARIAN EXTRAMEDULLARY LEUKEMIC RELAPSE IN YOUNG GIRLS. A REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE.

Cecalupo AJ, Frankel LS, Sullivan MP
(c/o Frankel) Dept. Pediatrics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 50(3):587-593 1982

Currently attention is focused on the testicle as a site of leukemic relapse. Leukemic involvement of the ovary has been described in several autopsy series with an incidence of 11-50% in patients with bone marrow relapse, but has rarely been reported during the clinical course of leukemia. In this report, four girls with childhood acute lymphocytic leukemia (ALL) who relapsed with a pelvic mass are presented. Three had marked ovarian infiltrates and the fourth had a presacral mass without ovarian disease. Involvement was also present in abdominal and pelvic lymph nodes, mesentery, omentum, and serosal surfaces. Two patients had infiltrates of the fallopian tubes and one had uterine involvement. Two patients had central nervous system disease and one patient had renal involvement at the time of relapse. Relapse occurred late in the course of disease. All patients had been in complete continuous remission prior to relapse. Retreatment was instituted in all patients and follow-up ranges from 18-135 mo from the time of pelvic relapse. All patients have maintained continuous bone marrow remission from the time of initial diagnosis, and one patient died 18 mo after ovarian relapse with significant extramedullary disease but no marrow involvement. This represents the first series of pelvic extramedullary leukemic relapse in females, an area of involvement that may be encountered more frequently in the future. (Author abstract) (42 Refs)

50. MUCORMYCOSIS IN LEUKEMIA.

Rosenberg SW, Lepley JB
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Oral Surg; 54(1):26-32 1982

Rhinocerebral mucormycosis is a virulent, rapidly progressive, potentially fatal illness which demands early diagnosis and aggressive medical and possibly surgical therapy. Although most commonly reported in persons with poorly controlled diabetes, it may occur in other immunosuppressed hosts. In persons with leukemia the disease has been uniformly fatal. A well-documented case of fatal rhinocerebral mucormycosis in a leukemic patient is presented to illustrate the diagnostic and therapeutic dilemmas often faced. A review of the 233 cases thus far reported in the literature is used as a spring-board for a discussion of the pathogenesis, diagnosis, and management of this disease. (Author abstract) (22 Refs)

SELECTED PRE-CLINICAL STUDIES

51. CHARACTERIZATION OF THE RECEPTORS FOR IGE ON MEMBRANES ISOLATED FROM RAT BASOPHILIC LEUKEMIA CELLS.

Isersky C, Rivera J, Triche TJ, Metzger H
Section Chemical Immunology, NIADDK, NIH, Bethesda, MD, 20205
Mol Immunol; 19(7):925-941 1982

Mast cells, basophils and a tumor analog, rat basophilic leukemia cells, have a surface receptor for immunoglobulin E (IgE). Membranes from such cells should be highly useful for the study of how the alpha- and beta-subunits of the receptor interact with the plasma membrane and function therein. Membranes were prepared from rat basophilic leukemia cells. The cells were reacted with radioiodinated IgE to saturate a fraction of their receptors and the radiolabel was used as a surface marker. When isolated from sucrose gradients, 40 +-10% yields of plasma membranes were obtained and these were typically purified 13-fold with regard to cellular proteins. Unoccupied receptors for IgE were almost all recovered (as assessed on membranes solubilized with detergent) as were surface-labeled proteins in general. The membrane-bound IgE appeared fully exposed as assessed with anti-IgE antibodies but surprisingly 70-80% of the unoccupied receptors present were unable to bind IgE when unsolubilized vesicles were tested. By electron microscopy the preparations appeared free of recognizable intracellular organelles. Though some of the membranes appeared multivesicular many showed large breaks in continuity. Assessment of permeability, carried out on dextran gradients, indicated that a significant number (greater than or equal to 50%) of the IgE-carrying membranes are not sealed. It is therefore most likely that both external and cytoplasmic aspects of the plasma membrane were exposed in many of the vesicles. Treatment of such membrane vesicles with trypsin or papain did not alter the apparent mol wt of the alpha-chain of the receptor or its binding activity for IgE. Additionally, when the vesicles were examined by enzyme-catalyzed iodination, no labeling of the receptor was observed under conditions where it is not labeled on intact cells (ie in the presence of IgE). These results suggest that either the alpha-chain of the receptor does not penetrate the membrane or that it cannot be modified by the particular probes we used. (Author abstract) (34 Refs)

52. EFFECTS OF ACLACINOMYCIN-A ON MURINE LEUKEMIA.

Nara N, Miyamoto T, Hirashima K, Momoi H
1st Dept. Internal Medicine, Tokyo Medical and Dental Univ., 5-45, Yushima 1-Chome, Bunkyo-Ku, Tokyo 113, Japan
Blood; 60(1):188-193 1982

Effects of aclacinomycin-A (ACM) on leukemic cells and normal hematopoietic stem cells were studied for the purpose of evaluating the usefulness of this agent as an antileukemic agent. ACM suppressed not only leukemic colony-forming unit (LCFU) in the radiation-induced murine erythroleukemia, but also normal hematopoietic stem cells (CFU-S, CFU-C) in mice. However, LCFU was the most sensitive to ACM. After the administration of ACM at a dose of 5 mg/kg, LCFU was suppressed to 0.02 of the control on Day 3 and recovered within 5 days. Splenic CFU-S and CFU-C were suppressed to the nadirs on Day 2 and Day 1, respectively, and they recovered within 5 days. On the basis of the differences in the sensitivities to ACM and recovery patterns between LCFU and normal hematopoietic stem cells, ACM at a single dose of 5 mg/kg was administered every 3 days (total dose of 25 mg/kg) into leukemic mice, and the increase in mean lifespan obtained 113.9%. Effectiveness of ACM in the treatment of acute leukemia was discussed. (Author abstract) (16 Refs)

53. TRANSPLANTATION OF LEUKEMIC BONE MARROW TREATED WITH CYTOTOXIC ANTILEUKEMIC ANTIBODIES AND COMPLEMENT.

Trigg ME, Poplack DG
Dept. Pediatrics, Univ. Wisconsin, Madison, WI, 53792
Science; 217(4556):259-261 1982

The ability of antiserum against murine L1210 leukemia to remove residual leukemia cells from murine bone marrow was investigated. Leukemic marrow was treated in vitro with antiserum and complement and used to hematologically reconstitute mice that had been irradiated with doses lethal to bone marrow. Following infusion of treated leukemic marrow, normal marrow returned without evidence of leukemia. More than 90 percent of the animals have survived for 11 mo without untoward effects, suggesting that the technique may be of use in the treatment of acute leukemia in humans. (Author abstract) (34 Refs)

REVIEWS

54. SURFACE MARKERS ON LEUKEMIA AND LYMPHOMA CELLS: RECENT ADVANCES.

Foon KA, Schroff RW, Gale RP
Biological Response Modifiers Program, NCI-Frederick Cancer Res. Facility, Building 560, Frederick, MD, 21701
Blood; 60(1):1-19 1982

Recent advances in immunology have led to important insights into leukocyte differentiation and the cellular origin of leukemia. It is now possible to precisely define stages of human lymphocyte and granulocyte differentiation utilizing highly specific monoclonal antibodies that define cell surface antigens in conjunction with more traditional markers such as surface and cytoplasmic immunoglobulin on B lymphocytes, sheep erythrocyte (E) receptors on T lymphocytes, and cytochemical staining of myeloid cells. Five major subtypes of acute lymphoblastic leukemia (ALL) are now recognized, including unclassified or null ALL, common ALL (cALL), pre-B-ALL, B-ALL, and T-ALL. Within the T-ALL subgroup, there is considerable heterogeneity based on the presence or absence of the E-receptor and various T-cell surface membrane antigens defined by monoclonal antibodies. Cells from patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and Sezary syndrome also can be classified by their reactivity with monoclonal antibodies. Acute myelogenous leukemia (AML) cells are generally classified by morphological and cytochemical features. Recently, monoclonal antibodies reactive with granulocytic and monocytic subtypes of AML have been developed. In addition to their utility in leukemia classification, monoclonal antibodies that identify leukemia associated antigens have also been used therapeutically. Monoclonal antibodies have been infused intravenously into patients with leukemia and lymphoma. They have also been used in vitro with complement to lyse residual leukemia cells from remission bone marrows removed from leukemia patients. These treated bone marrows were later reinfused into the same patients to 'rescue' them following high-dose chemotherapy and radiation therapy. (Author abstract) (203 Refs)

55. CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA: A REVIEW.

Willoughby ML
Dept. Haematology, Royal Hosp. for Sick Children, Yorkhill, Glasgow G3 8SJ, Scotland
J R Soc Med; 75(6):464-473 1982

Management, prognostic factors, long-term side effects of treatment, and outstanding problems in the treatment of acute lymphoblastic leukemia (ALL) in children are reviewed. The basic plan of therapy of ALL involves induction of initial complete remission, preventive therapy against development of CNS infiltration, and multi-drug maintenance chemotherapy for an extended period in the hope of eradicating all leukemic cells or progenitors. The height of WBC, or of the circulating blast cell count, at diagnosis has come to be the most widely-used single prognostic factor stratifying above or below 20,000/cubic mm, or in more recent United States trials, at 10,000 and 50,000. (82 Refs)

56. ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDHOOD.

Alvarado CS, Kim T, Ragab AH
(c/o Ragab) Section Pediatrics, Emory Univ. Clinic, 1365 Clifton Road, N.E., Atlanta, GA, 30322
J Med Assoc Ga; 71(4):289-292 1982

Diagnosis, classification, prognostic factors, management, improved survival, and new directions in the treatment of acute lymphoblastic leukemia (ALL) in childhood are discussed. The diagnosis of ALL is often suggested by an abnormal blood count, but can be only firmly established or discarded by a bone marrow aspirate. The differential diagnosis includes four main entities. The prognostic value of immunologic subsets is demonstrated by the positive correlation with clinical and laboratory features associated with prognosis. The improved results in the treatment of ALL are in part due to the progress made in the area of chemotherapy and supportive care. (10 Refs)

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